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PRIMARY MALIGNANT TUMORS OF THE LONG BONES

END-RESULTS IN ONE HUNDRED AND SEVENTY OPERABLE CASES, INCLUDING A SMALL GROUP OF MALIGNANT CENTRAL SARCOMA *

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Periosteal sarcoma of the long bones has long been recognized as one of the most malignant of all tumors. The prognosis in this type has been regarded by surgeons as practically hopeless, even early amputation at the proximal articulation rarely saving the life of the patient. With the advent of the roentgen ray—which was soon recognized as the greatest aid to the surgeon in making an early diagnosis—it was hoped that better results would be obtained by reason of earlier amputation. These hopes, however, have not been realized, and in spite of early amputation, practically all the patients have died of metastases within a few months or a year after the operation.

The end-results of operative treatment of sarcoma of the long bones, as reported at a symposium on long bone sarcoma before the Royal College of Surgeons in November, 1912, and a second symposium before the Association of British Surgeons in May, 1923, showed practically no improvement over the gloomy statistics of Butlin, published a generation ago. A few surgeons, notably Bloodgood,[1] following the lead of Paget and Nélaton, believe that giant cell sarcoma is practically a benign lesion and that these cases should be treated by conservative methods; i. e., preferably curettage, followed by the application of phenol (carbolic acid) and zinc chloride, occasionally by resection and only rarely by amputation. On the other hand, Bloodgood [2] believes that periosteal

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[ED. NOTE:—This article, because of its great length, has been divided into two parts; the second part, containing the case reports and illustrations, will appear in the January issue.]

*Read in part before the annual meeting of the Association of British Surgeons, London, May, 1923, and before the American Surgical Association, Washington, D. C., May 5, 1925.

*This series of 170 cases includes periosteal sarcoma, subperiosteal sarcoma, the type of tumor characterized by most pathologists as round cell sarcoma and by Ewing as endothelioma, and a small group of malignant central tumors.

1. Bloodgood, J. C.: Ann. Surg. **69**:345 (April) 1919.
2. Bloodgood, J. C.: Am. J. Surg. **37**:105 (May) 1923.

sarcoma is so malignant that amputation rarely saves the life of the patient (probably only 2 per cent of the patients recover) and therefore he seldom, if ever, advises amputation in this type of tumor. Until comparatively recent years, however, surgeons in general have continued to amputate the limb for practically all types of sarcoma of the long bones. With the advent of radium, in sufficient quantities, and further, with the introduction of the high voltage roentgen-ray machine, it was hoped that we should see better results, especially in the osteogenic type of sarcoma of the long bones.

At the Memorial Hospital during the last ten years we have been fortunate enough to have at our disposal an ample supply of radium, and we have made a careful attempt to ascertain the value of this agent in the treatment of long bone sarcoma of all types. During this period, we have been treating different groups of cases by different methods and combinations of methods, i. e., radium alone, roentgen rays alone, toxins alone, toxins and radium, amputation alone, and amputation followed by toxins. (The majority of patients treated during this period have been treated by radium or roentgen rays.) It is the end-results obtained in this series of cases that we desire to report.

At present the surgeons are divided into two fairly definite groups as regards the treatment of sarcoma of the long bones: one group amputates in every case as soon as the diagnosis has been made, regardless of the type of tumor (central or periosteal) or the morphology (giant cell or osteogenic), and the other, never amputating, believes this to be an inefficient and unwise procedure in periosteal sarcoma, as in any event the patient dies; they also believe that central tumors are better treated by conservative methods. If we were suffering from sarcoma of a long bone, we should much prefer to fall into the hands of a surgeon belonging to the first group whose members always amputate rather than of one belonging to the second, whose members never amputate. With the advent of radium and the high voltage roentgen-ray machine, the ranks of the second group are rapidly increasing in number, and fewer and fewer cases of periosteal sarcoma are being subjected to amputation for the reason that strong hopes are entertained that radium or roentgen rays will cure or retard the progress of the disease for a considerable period of time. Whether these hopes are justified, it is, perhaps, too early to say positively, but our results may help to answer the question.

Then there is a third group of surgeons, few in number at present but slowly increasing, who believe that the problems involved in the treatment of sarcoma of the long bones differ so widely that no one hard-and-fast rule that will cover every case can be laid down. This group believes it is wise to make a careful study of each individual case especially as regards diagnosis and to be guided in the selection of treatment to be employed by the results obtained in similar cases.

So far there has been no large series of patients (except those treated by amputation) treated by different methods and traced for a sufficient period of time to permit conclusions of material value to the surgeon. It was in the hope of supplying, in a measure, the necessary data that the present article was written. We believe that a large proportion of patients are now being treated primarily by radium or roentgen rays, and yet the surgeon who advises the treatment probably has no definite idea of the prognosis such treatment offers. He has a fairly firm conviction that amputation offers little or no hope of a cure, and hence he is willing to try any other method that may retard the progress of the disease and possibly save some lives. His decision is based on hopes rather than on facts or any definite knowledge of the end-results of roentgen-ray or radium treatment.

During the last ten years, we have observed a large number of cases in which roentgen-ray or radium treatment has been the primary method of choice and the end-results have been carefully followed up. A distinguished pathologist recently told us that if he ever had a sarcoma of the long bones he would have an immediate amputation regardless of the histologic type of the tumor. Shortly after this a distinguished surgeon made the statement that he had performed his last amputation for long bone sarcoma. In the face of such widely divergent opinions, it is all important that the facts bearing on the diagnosis and end-results of different methods of treatment should be most carefully compiled and published in some detail. It is only by a careful study of these facts that it is possible to form any definite or intelligent conclusions as to the best method of dealing with the condition. At the London symposium on long bone sarcoma in 1923 one of the members stated that long bone sarcoma was so rare that some might question the wisdom of devoting so much time to a discussion of the subject; he estimated that there were only 400 cases in England. While it is true that the condition is a rare one, it is none the less true that when it does occur, it usually occurs in the finest and most healthy specimens of young adult life; therefore we feel stimulated to put forth our best efforts to save these young lives. The very fact of the rarity of the condition has rendered advance in its treatment difficult. The average surgeon may see but one case in a year, or less, and the surgeon of large general hospital experience may see no more than two or three during a year; he does not see enough cases or follow the end-results sufficiently long to enable him to decide from his own experience what method offers the best chance of saving the patient.

The opinions of even experienced surgeons as to the best methods of treating long bone sarcoma are at the present time so widely at variance that the whole subject is in a state of confusion; the result is that in a given case of sarcoma of the long bones the surgeon is utterly unable to decide what form of treatment to advise.

While the Bone Sarcoma Registry, to which Dr. E. A. Codman has devoted much time and energy for several years, will undoubtedly prove of great help in enlarging our knowledge of the diagnosis and pathology of the disease, so far it has been of little aid in deciding on the best methods of treatment; neither does it furnish any accurate idea of the prognosis of the different types of bone sarcoma. It is quite natural and easy to understand that the average surgeon is far more inclined to go to the trouble of compiling the necessary data (clinical history, roentgenograms, microscopic slides) to register a successful case than he would be to register an unsuccessful one. For this reason, the relative proportion of successful cases in such a collection as the Bone Sarcoma Registry will be greater than the normal rate, as found in a series of consecutive, unselected cases observed at a single clinic or by a single surgeon. This is well shown in the group of giant cell sarcoma. Bloodgood,[3] in his latest article on giant cell tumor, has added 100 cases from the Bone Sarcoma Registry to his own personally observed series of cases and uses this compilation to show that giant cell sarcoma is practically always benign. While his statistics may suffice to prove in theory that giant cell sarcoma is quite a benign affair, the memory of the ten patients with tumors pronounced benign giant cell by experienced pathologists [4] who later died of metastases, and one additional similar case that has likewise proved fatal, has served to convince us that giant cell sarcoma may be a real "specter."

It is interesting to note that the article of McWhorter and MacGuire [5] containing the end-results of fifty consecutive cases observed at the New York, Presbyterian and Bellevue Hospitals shows almost exactly the same percentage of malignant giant cell tumors as our own series, i. e., one in five.

We cite these cases merely to show that it is impossible to obtain a true idea of the prognosis of bone sarcoma from scattered cases reported in the literature or even from those compiled by bone sarcoma registries. Up to the present time, there has been no large series of cases of bone sarcoma in which treatment with roentgen rays or radium has been systematically carried out in a sufficient number of cases or for a sufficient length of time to permit any conclusions as to the curative value of these agents in bone sarcoma. The unusually large amount of clinical material at the Memorial Hospital supplemented by that of the Hospital for Ruptured and Crippled for more than thirty years has made it possible to

3. Bloodgood, J. C.: Giant Cell Tumor of Bone and the Specter of the Metastasizing Giant Cell Tumor, Surg. Gynec. Obst. **38**:784 (June) 1924.

4. Coley, W. B.: Prognosis in Giant Cell Sarcoma of the Long Bones, Ann. Surg. **79**:321 (March) 1924.

5. McWhorter, J. E., and MacGuire, C. J., Jr.: Sarcoma of Bone, Arch. Surg. **9**:545 (Nov.) 1924.

report a series of upwards of 170 operable cases of malignant subperiosteal sarcoma treated by different methods, nearly all of which were traced to end-results. Furthermore, we have had at our disposal at the Memorial Hospital during the last ten years an unusually large amount of radium and, in addition, several high voltage roentgen-ray machines installed in recent years. Still further, we have had the benefit of Dr. James Ewing's wide experience in the study of the pathology of these tumors. The end-results in this series of cases, while in no way expected to furnish a complete solution of the problem of treatment, are sufficient, in our opinion, to throw some light on it and to aid us in the selection of the best method of treatment.

TABLE 1.—*Location of Tumor in Present Series of Cases*

		Proximal	Shaft	Distal
Femur	71	8	17	46
Tibia	32	18	11	3
Humerus	38	28	7	3
Fibula	6	4	0	2
Radius and ulna	11	1	3	7
Clavicle	8			
Metatarsal	2			
Metacarpal	1			
Ribs	1			

TABLE 2.—*Age of Patients*

	Patients
Up to and including 5 years	2
6 to 10 years	16
11 to 20 years	67
21 to 30 years	41
31 to 40 years	27
41 to 50 years	11
51 to 60 years	3
Over 60 years	3
Sex: 95 males, 75 females.	170

METHODS OF DIAGNOSIS

No plan of treatment should be outlined until every effort has been made to arrive at an accurate diagnosis. A careful history of the case with special reference to antecedent local trauma, duration of the tumor and, most important of all, a history of pain, persistent and increasing in severity, will prove of great help in making a diagnosis of sarcoma of the long bones. The roentgenogram may be so characteristic that it will be possible to make a positive diagnosis from that alone, especially in the periosteal osteogenic cases. In certain other cases, the roentgenogram may be of great help but not a decisive factor in making a diagnosis. A typical periosteal sarcoma in the early stages presents the following clinical picture: trauma occurring from a few days to a few months before the appearance of the tumor (in 50 per cent of the

cases); pain appearing several days or weeks before the tumor is noticed and increasing in severity, often becoming worse at night; an immovable tumor, apparently connected with the bone or periosteum, of firm but not bony consistency; skin normal in appearance and not adherent, and slight local heat. In the later stages, the skin becomes thin, and the superficial veins are dilated; but a diagnosis should be made long before this condition is apparent if the life of the patient is to be saved by any method of treatment.

Pain is the first and most important symptom. It nearly always precedes the appearance of a swelling or tumor by a longer or shorter interval—a few days, a few weeks or, in some rare cases, several months. The pain is dull and persistent, often worse at night, and frequently most severe at a considerable distance below the site of the tumor. Early pain before the development of a tumor or swelling has resulted in most of these cases being regarded as of rheumatic origin, and in their being treated accordingly. Severe, persistent pain in any long bone of a healthy, young adult who is between the ages of 15 and 30, especially when it follows a recent trauma, should immediately arouse a suspicion of sarcoma and entitle the patient to frequent physical examinations supplemented by frequent roentgen-ray examination.

A number of pathologic conditions may simulate sarcoma of the long bones more or less closely.

MYOSITIS OSSIFICANS

This condition causes greater difficulty in diagnosis than perhaps any other lesion of the long bones. Fortunately it is a very rare condition. One of us [6] reported several cases and described the differential diagnosis of this condition and sarcoma, at the same time pointing out the fact that in nearly every case it was possible to make a differential diagnosis by the roentgenogram and the clinical history of the case.

The clinical history in a case of myositis ossificans is fairly characteristic; swelling usually follows a rather severe injury, such as a football injury. The locality of the swelling is most often the region of the quadriceps muscle of the anterior portion of the thigh. The tumor develops rapidly during the first three or four weeks, after which there is a period of apparent quiescence, when there is little noticeable change. Severe pain, which is often associated with periosteal sarcoma, is seldom present in myositis ossificans. In consistency, the tumor is of a peculiar bony hardness in contradistinction to the firm but more or less resilient "feel" of periosteal sarcoma. In myositis ossificans the roentgenogram shows an intact and sharply defined periosteal line, whereas in periosteal sarcoma, even in the early stages, some break in the line will nearly always be noticed, in the way of indentation, or irregularity, or a slight splitting-up of the periosteum. We have observed only two cases of periosteal sarcoma in which the periosteal line was intact. In one of

6. Coley, W. B. C.: Myositis Ossificans Traumatica, Ann. Surg., March, 1913.

these cases, which was in an early stage of the disease, it was possible, from the clinical history and in the absence of trauma, to make a diagnosis of sarcoma rather than of myositis ossificans, and this diagnosis was confirmed by microscopic examination. The second case gave a history of an apparently slowly growing tumor of two years' duration following a severe injury. The tumor was situated in the lower end of the femur rather than in the shaft. While the clinical history and roentgenogram pointed to a sarcoma, strange to say, the microscopic sections showed only a productive osteitis or myositis ossificans; this case later proved to be a sarcoma, which metastasized and finally ended in death.*

The rapidity of the growth in periosteal sarcoma varies greatly. The sclerosing type may go on for two or three years or more before attaining a large size; but such cases are extremely rare. On the other hand, the tumor may grow so rapidly as to reach a large size in the short space of three or four weeks, and may destroy the life of the patient in a few months.

OSTEOMYELITIS

In syphilitic osteomyelitis the shaft of the bone is more frequently involved than the extremities, and the lesion is usually characterized by a definite hyperostosis or thickening of a considerable area of the diaphysis. The new bone formation is much more dense than that found in periosteal sarcoma. A type of sarcoma that is usually found in the shaft of the bone in one that has been designated by Ewing as endothelioma with little or no new bone formation; this can be differentiated from syphilitic osteomyelitis in that in the latter condition the progress of the disease is slower, and the pain so characteristic of sarcoma is usually absent. There are certain cases of acute or subacute osteomyelitis which it is almost impossible to differentiate from sarcoma, even with the aid of roentgen-ray examination, and sometimes with the additional help of exploratory operation and microscopic study. Three cases of this kind have recently come under our observation. In none was the correct diagnosis made even with the aid of a careful clinical history and roentgenograms supplemented by exploratory operation and microscopic examination. In two of these cases, the question arises as to whether the original condition might not have been an osteomyelitis, and the sarcoma an independent and later condition superimposed on the original osteomyelitis. We are inclined to believe that the original condition was an atypical sarcoma at least in one of the cases.

In a young man, a primary tumor was removed from the lower end of the femur and pronounced an osteoma; it recurred shortly afterward and ten years later it took on signs of malignancy. It was then possible

*There is another important differential diagnostic feature which previously we have not seen mentioned. Whereas in periosteal sarcoma the roentgen-ray picture shows that new bone or tumor extends around or nearly around, the long bone; in myositis ossificans it is confined to one portion and rarely extends more than one-half the circumference of the bone.

to make a roentgen-ray and clinical diagnosis of sarcoma. Amputation was performed and microscopic examination showed the tumor to be an osteosarcoma with a large amount of ivory-like new bone. In spite of prophylactic toxin treatment, the patient, after remaining well for three years, died of metastases of the lung. In another case, an adult male sustained a fracture of the central portion of the shaft of the femur at the age of 4 years, and another fracture at the same site seven years later. A more or less chronic osteomyelitis developed and continued for nearly twenty-seven years, when a rapidly growing tumor, was noted at the same site; this proved to be a periosteal sarcoma. Amputation was performed at the hip joint, followed by prophylactic toxin treatment. The patient is alive and well nine and one half years later (case 18).

In these two cases, we believe it is fair to assume that the old osteoma furnished a favorable soil for the development of a sarcoma many years later in case 1, and in the other case, that a chronic osteomyelitis developed at the site of an old fracture and proved a favorable site for the sarcoma that developed many years later.

TUBERCULOSIS

Tuberculosis of the bones has often been mistaken for sarcoma, and vice versa; yet a careful history and thorough physical examination aided by a roentgenogram should enable one to make a differential diagnosis in the great majority of cases. Generally speaking, the two conditions show striking points of difference as well as similarity. They are both apt to occur in young adults; they have a predilection to the extremity of the bone rather than the shaft; there is often a history of local antencedent trauma in both conditions. They differ in the following important points: Sarcoma, as a rule, occurs in young adults who give every evidence of being in the best of health, whereas tuberculosis of the bones is more commonly found in persons whose general condition is below par. An evening rise of temperature is often noted in tuberculosis of the bones; while it may be noted in sarcoma, it is unusual. The duration of the disease is usually longer and its progress slower in tuberculosis than in sarcoma. Pain may be an important symptom in both conditions but it is usually more severe and persistent in sarcoma. The most important point of difference is the location of the disease: sarcoma practically never begins in the epiphysis of the bone, whereas tuberculosis nearly always begins in the epiphysis and involves the joint in the comparatively early stages of the disease. In tuberculosis, the skin is paler than normal whereas in sarcoma, even in the comparatively early stages, the skin is redder than normal, often of a purple hue, due to dilatation of the superficial vessels.

The diagnosis of tuberculosis cannot always be made from the clinical and roentgen-ray evidence as was pointed out by Beye,[7] who reported two cases diagnosed as osteosarcoma but which at necropsy proved to be tuberculosis. If these patients had recovered, the claim doubtless would have been advanced that two periosteal sarcomas of the long bones had been cured by the agents employed.

TRAUMA AS AN ETIOLOGIC FACTOR IN CASES OF LONG BONE SARCOMA

Those who still refuse to believe that trauma has an important causal influence on the development of a malignant tumor base their opinion on the theory that the tumor was already present at the site of the injury and had escaped the notice of the patient until the time of the injury. This would assume not only an uncommon ignorance and lack of personal observation on the part of the patient, but in many cases a similar ignorance and lack of observation on the part of the physician who had attended the patient at the time of the injury and who had failed to find any swelling or evidence of a tumor at that time. If a swelling develops at the exact site of an injury, within a few days or weeks or months thereafter, and develops the typical clinical characteristics of a sarcoma, the diagnosis being further supported by microscopic examination, and finally causes the death of the patient, it seems illogical and difficult to nullify or minimize the influence of the injury by the assumption that a malignant tumor was already present at the exact site of the injury but without any previous symptoms or physical signs.

In addition, we have a number of cases in which it is not necessary to decide the question on the powers of observation on the part of the patient or on the part of the physician. The roentgenograms taken at the time of the accident furnish conclusive evidence that there was no pathologic lesion of the bone at the time of the accident, and yet a very malignant sarcoma developed within one or two weeks at the exact site of the injury. These cases, especially cases of recent fracture showing a rapidly growing sarcoma appearing from a few weeks to a couple of months after the injury, furnish, in our opinion, absolute proof that the injury was the causative factor. It is not necessary to be able to explain the exact manner in which trauma may cause the development of a malignant tumor in order to admit its causal influence.

We believe, and more strongly with increasing experience, that all types of malignant tumors are of extrinsic origin. It is not improbable that it may some day be proved that what we have hitherto included under the vague term "hereditary influence" may some day be proved a

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7. Beye, H. L.: Errors in the X-Ray Diagnosis of Osteogenic Sarcoma, Ann. Surg. **80**:730 (Nov.) 1924.

micro-organism or virus, as has already been proved in tuberculosis, and that the only thing inherited is tissues less resistant to the virus or infection. Whether we accept the parasitic theory of cancer or still believe in its intrinsic origin, we must admit that trauma plays a direct and important part in the development of cancer and especially of bone sarcoma. The argument advanced by some writers that, if such were true, all cases of trauma or a larger proportion of cases ought to be followed by the appearance of a cancer, is not logical. If fifty people were plunged into an icy pond and only two developed pneumonia, by the same reasoning we might say that, because forty-eight remained well, the shock and exposure were not causative factors in the development of the pneumonia in the two who contracted it. The exposure to cold simply lowered the resistance of the body and prepared a favorable soil for the development of the pneumococcus.

Since this article was written, the more important work of Gye and Barnard of London has been published, and the micro-organism that they have discovered has been widely accepted as the cause of malignant tumors. The earlier and important research work of Glover and Scott of New York, and Nuzum of Chicago, as well as Young of Edinburgh, furnishes strong evidence in support of this view.[8]

Clinical evidence and experimental researches have shown that trauma is an exciting factor in a large proportion of cases of tuberculosis of the bone. Recently Schmidt has shown that nearly 30 per cent of the cases of acute osteomyelitis have a history of antecedent trauma.

The present series of 170 cases shows a history of definite antecedent local injury in eight-seven cases, or slightly over 50 per cent. This is almost identical with the percentage found by Gross in his series of 160 compiled cases of sarcoma of the long bones published in 1879. Our recent report of fifty cases of giant cell sarcoma showed a history of antecedent local trauma in 56 per cent. Kolodny in his recent paper on bone sarcoma found a history of antecedent local trauma in 70 per cent of patients over 10 years of age.

The interval elapsing between the injury and the development of the tumor is important. In the present series it is shown to be as follows: few days, six cases; one week, five cases; from two to three weeks, twenty-four; from three to four weeks, six; six weeks, one; two months, nine; three months, three; six months, four; ten months two; thirteen months, one; eighteen months, three; two years, three; fours years, three; five years, one; from six to seven years, one; ten years, one; fourteen years, one, and more than twenty years, one (osteomyelitis).

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8. Sebestyén has written a long paper on trauma in connection with bone sarcoma, Arch. f. klin. Chir. **136**:4, 1925. He believes that there can be no question that trauma is a causative factor in bone sarcoma.

The influence of trauma in sarcoma of the bone has been discussed further by one of us (W. C. B.) in another article (Internat. J. Surg. **39:** 259 [July]; 318 [Aug.] 1926).

EXPLORATORY OPERATION

During recent years there has been a tendency to emphasize the dangers of exploratory operation in tumors in general, particularly in tumors of the long bones, with the result that many surgeons have discontinued this practice. We believe that the dangers have been greatly overestimated. While it is true that in a number of cases the clinical and roentgen-ray findings are sufficiently clear to establish a definite diagnosis, on the other hand, there are certain cases, particularly those in the early stages of the disease when proper treatment is most likely to be of avail, in which it is extremely important to make an accurate diagnosis before it is possible to do so by the clinical and roentgen-ray evidence alone. In such cases, we believe exploratory operation is of great value and is attended with comparatively little risk. These cases will be found chiefly in the periosteal group; the tumors are not extremely vascular and the exploratory incision practically always heals by primary union with little or no risk of infection. In the central group, exploratory operation is usually and should be always associated with complete curettage, thereby greatly increasing the chances of controlling the growth by subsequent toxin and radium treatment after currettage.

Littlewood[9] of Leeds, England, emphasizes the importance of exploratory operation in long bone sarcoma. As he states,

> So often we wait to see if the condition is inflammatory when an exploratory operation would clear up the doubt. During recent years, I have explored four cases of enlargement about the lower end of the femur, thinking they might be sarcoma and then found them to be traumatic periostitis associated with some myositis ossificans.

We have recently had a similar case at the Hospital for Ruptured and Crippled. This patient, a man, with an indefinite history of injury, was transferred to our service from the orthopedic department. There was a tumor of the femur of about seven months' duration, not associated with any temperature or other signs of inflammation. Roentgen-ray examination showed an apparent osteogenic periosteal sarcoma with considerable new bone formation. Exploration, however, revealed in addition to the new bone formation a considerble quantity of seropurulent fluid, which bacteriologic examination showed to be caused by *Staphylococcus aureus* infection. Exploratory operation in this case was the best possible form of treatment, for had we used roentgen rays,

9. Littlewood, H.: Amputation at the Shoulder and at the Hip, Brit. M. J. **1:**381 (March 11) 1922.

radium or toxins for a considerable period, until the diagnosis had been established, the infection in the meantime would have caused greater destruction of the femur (case 35).

The opposition to exploratory operation in sarcoma of the long bones is based on two assumptions: (1) the danger of serious infection following the operation, and (2) the danger of generalization of the disease. While there undoubtedly are a few cases in which infection has followed exploratory operation and necessitated amputating the limb in order to save the life of the patient, these cases, we believe, have practically all occurred in the central group, and before the introduction of the surgical solution of chlorinated soda (Dakin's solution).

If we are dealing with a central sarcoma or a giant and spindle cell sarcoma, simple exploratory operation should never be performed, but rather should be an important part of the treatment itself; that is, as much of the tumor as possible should be removed with a curet and the cavity swabbed out with chloride of zinc or phenol. As soon as possible thereafter, the patient should be put on the mixed toxins of erysipelas and *Bacillus prodigiosus,* supplemented if possible with either radium or roentgen rays. Our experience shows that patients treated in this way have better results and show more prompt recovery of function than those treated with roentgen rays or radium alone.

In the present article, however, we are chiefly concerned with periosteal sarcoma. Exploratory operation in these cases is nearly always followed by primary wound healing with scarcely ever any infection. In a few cases of central malignant or telangiectatic sarcoma the wound may fail to heal promptly and may become the site of a rapidly growing fungating tumor, later necessitating amputation. Amputation should be performed as soon as the diagnosis is made and not after prolonged treatment. As to the second danger of producing generalization of the disease by the exploratory operation, we believe the risk almost entirely theoretical. The fact that an exploratory operation was performed in nearly all our cases in which the patient was cured shows that in these cases at least the operation did no harm. We have never seen a case in which there was good reason to believe that the operation hastened the development of metastases.

We have observed a case of chondrosarcoma of the humerus in which exploratory operation showed a tumor of the upper end of the humerus; roentgen-ray treatment was given for a period of five months, during which time the tumor rapidly increased in size and became fungating; finally amputation was performed when the disease had nearly reached the stage of inoperability, and it was necessary to give the patient transfusion before amputating. After the operation, the patient remained well for over a year; but in July, 1925, he developed metastases of the lung, and died a few weeks later. Had the amputation been

performed immediately after the exploratory operation, the chances of a cure would have been much greater.

It is often important to know the type of tumor with which we are dealing in order to advise the method of treatment most likely to effect a cure or the greatest amount of alleviation. In the typical case of sarcoma of the long bones, the clinical history and roentgenograms will enable one to make a positive diagnosis in a fairly early stage of the disease; and in these cases we would not advise exploratory operation. There are other cases, however, in which we cannot make a positive diagnosis in the early stages without an exploratory operation, and in these cases we regard biopsy as of the greatest possible value. In illustration of this point we would cite cases 13, 23 and 35.

In a doubtful case in which it is impossible from the clinical and roentgen-ray data to determine whether the condition is one of osteomyelitis, myositis ossificans or sarcoma, shall we go on with the roentgen ray or radium treatment until the clinical and roentgen-ray signs make the diagnosis clear? Our experience shows that by following this course, not infrequently metastasis of the lung or generalization of the disease occurs before it is possible to establish the diagnosis, even though distinct local improvement may be taking place. On the other hand, is there any sound reason why we should not perform a comparatively safe exploratory operation, at once gaining thereby the valuable information which the exploratory incision and a microscopic study of the sections afford?

As stated before, the danger of infection following exploratory operation in periosteal sarcoma should be comparatively nil for the reason that should the microscopic examination show the tumor to be an osteogenic sarcoma with much new bone formation, then immediate amputation should be performed, followed by the use of the toxins. In this case, there would be little chance for infection to occur. Furthermore, exploratory operation should never be advocated as a routine practice by any surgeon but it should be performed only by the surgeon who is to take charge of the final treatment of the case. The gross appearance of the bone, as revealed by exploratory operation, will often give as much or more information to the surgeon who has had long experience with bone neoplasms as the microscopic picture itself, and he should have the benefit of both.

From a practical point of view, it would be interesting to know in how many of the more than fifty cases of the present series in which the patients are living an exploratory operation was performed. We find this to have been the method of procedure in twenty-seven of the thirty-five cases in which the patients are well from three to twenty-eight years, showing that exploratory operation in this group did not interfere with the chances of curing the disease.

It must be admitted that there are certain cases in which it is impossible to make a definite diagnosis from the clinical history and roentgenograms even when supplemented by a microscopic examination of the section by a competent pathologist; but these cases are rare exceptions, and should not influence us in our attempt to formulate a general rule.

The fact has often been emphasized by Ewing and others that even with all the modern aids to early diagnosis, an early diagnosis of sarcoma of the long bones, or of bone sarcoma in general, is seldom made even by experienced surgeons. While we may agree that in the majority of cases of bone sarcoma, a correct diagnosis can be reached from a careful clinical history and the roentgen-ray findings, this can only be done by one who has had much experience in this disease. One of the great difficulties lies in the fact that the average surgeon sees but a few during many years of practice, and never a sufficient number to enable him to become familiar with the many types of the disease.

METHODS OF USING RADIUM

Up to 1916 when radium was first used in the treatment of sarcoma of the long bones at the Memorial Hospital, the supply was very limited. It was used in the form of a small plaque with silver and lead filtration; this was placed near the surface of the skin, not more than 0.5 cm. distance from it. Superficial burns resulted from this method of application, and little effect was noticed on the tumor, with the exception of one case. In 1916, when the Memorial Hospital received a gift of a large amount of radium, we began to use it in the form of a pack containing from 1 to 2 Gm. filtered by 0.5 mm. of silver, and 2 mm. of lead, later changed to brass, and placed from 6 to 10 cm. from the skin. From time to time the dose has been varied. In the earlier cases we ordinarily gave from 10,000 to 20,000 millicurie hours at 10 cm. distance at a single treatment, repeating this from four to six weeks later. In a case of sarcoma of the femur, as high as 50,000 millicurie hours divided over three areas, anterior, posterior and lateral, about 17,000 millicurie hours over each, have been given as a single treatment covering a period of three to four days. This patient developed extensive generalization of the disease within two months.

In 1917, we began using bare tubes of unfiltered radium inserted through a hollow needle into the depths of the tumor. At first the dose was limited to from 10 to 25 millicurie hours; but during the last year, as high as 78 millicurie hours of unfiltered radium in bare tubes was used in a case of periosteal sarcoma of the shaft of the femur. This large dose had a very slight and only very temporary retarding effect on the tumor; in spite of additional very heavy radiation given in the form of a pack, the disease continued to progress, causing death about two

months later. In several other cases, a combination of bare tubes and radium-pack treatment was employed.

The largest amount of radium in the form of a pack thus far used by us at the Memorial Hospital was 150,000 millicurie hours spread over a period of nearly two years. In this case, a giant cell sarcoma of the femur, the patient made a complete recovery and is still well five years later. While in this case no burn followed the use of the radium, the joint became practically ankylosed, the skin became bronzed and of a leathery texture, and the bone was apparently rendered more brittle, as two years later following a slight injury a fracture occurred just above the site of the previous tumor of the femur. It is interesting to note that in this case union was very much delayed, and the patient's disability extended for more than a year. Undoubtedly, too large a dose of radium had been used. In another case, a periosteal sarcoma of the femur, in which a large amount of radium and roentgen rays was used, the lower part of the femur just above the site of the tumor became so markedly sclerosed that a fracture occurred while the patient was lying in bed. The disease was not controlled even by this large amount of radium. In a case of periosteal sarcoma of the femur, 209,000 millicurie hours were used in the short space of two months by one of our colleagues; the lesion was not controlled.

We do not believe it is possible at the present time accurately to estimate the exact amount of radium or roentgen rays the skin is able to stand without being seriously damaged or without causing serious endarteritis of the deeper vessels. In view of the fact that very serious results may follow the use of too large amounts of radium or roentgen rays, we believe it is most important to keep within the safe limits.

At present we have no evidence to prove that the introduction of bare tubes in bone sarcomas produces any better results than the application of external radiation in the form of a pack. Recently, gold plated bare tubes have been used at the Memorial Hospital with marked benefit in tumors of other parts of the body, particularly the tongue; the gold plate shuts off many of the beta rays and permits the use of a larger dose without causing sloughing or destruction of tissue. It is possible that this method may offer some advantages over the ones previously tried.

The only cases of periosteal sarcoma that we have been able to find in the literature in which the tumors have disappeared under radiation and the patients have remained well five years are the three cases reported by Dr. A. E. Hayward Pinch, medical superintendent of the Radium Institute of London. Jan. 6, 1926, he stated:[10]

> My two cases of periosteal sarcoma are still alive; one was treated in June, 1913, and the other in February, 1914. The nature of the disease had been veri-

10. Pinch, A. E. H.: Personal communication to the authors.

fied in each case by microscopical examination before the radium treatment was given, and reported as definite periosteal sarcoma. Incidentally, I heard of a third case six months ago, a lad whom I treated in 1911 for periosteal sarcoma of the thigh. He is now a captain in his majesty's army and in perfect health. As regards osteogenetic sarcoma, I have no good cases to report; this type of disease seems nonamenable to effective radium treatment.

In our opinion, the cases (reported) by Dr. Pinch must have been of the round cell or endothelial (endothelioma, according to Ewing) type, and not osteogenic sarcoma. Pinch's cases were all treated by the introduction of silver tubes into the tumor, which were then removed.

EFFECTS OF PROLONGED IRRADIATION

We are just beginning to appreciate some of the disadvantages and dangers of prolonged radiation, especially in cases of bone tumors. These results show how far we are at present from an understanding of the most efficient and, at the same time, safe dose of radium or roentgen rays. In the great majority of cases of periosteal sarcoma of the long bones, death has occurred before there has been an opportunity of observing the later effects of prolonged radiation; but we have had a few patients who survived sufficiently long to show certain important pathologic changes. In several cases marked changes in bone have taken place; i. e., the bone has been transformed into a hard, ivory-like tissue, exceedingly brittle, and prone to fracture under little or no strain.

In some of our cases the limb has been amputated, thus affording an opportunity for a careful macroscopic and microscopic study. In some instances we have found the marrow cavity almost completely obliterated or transformed into an ivory-like tissue, exceedingly brittle; in the event of a pathologic fracture this bone, by reason of the obliteration of the blood vessels, has shown little power to form new callus or to initiate the normal process of repair. In addition to the changes in the bone, we have found marked changes in the soft parts consisting of general endarteritis, complete occlusion of many of the smaller vessels, with marked fibrosis and transformation into a leathery tissue. In some cases, these changes brought about by overradiation are accompanied by severe pain. In one case of giant cell sarcoma of the femur, a small area of ulceration about three-fourths inch (1.8 cm.) in diameter developed two years after treatment, accompanied by severe pain. Whether the pain was due to the ulceration or to the general endarteritis, it was impossible to say; but it became so severe that amputation had to be performed about eight months later. Although the amputation was done about 6 inches (15.2 cm.) above the area of maximum radiation, the soft tissues over the stump recently became greatly thickened and extremely painful so that it was necessary to perform a second operation for the removal of this abnormal tissue, which was about 1 inch

(2.5 cm.) in thickness and so hard that it was almost impossible to cut it with a knife. In another case, referred to by one of us [11] and reported in full by Bancroft,[12] the patient was treated with roentgen rays following curettage for a small benign giant cell tumor of the radius. Although the disease was cured, the resultant pain and osteomyelitis of the bone from overradiation made it necessary to resect the radius and ulna (fourth operation performed), leaving a much impaired hand.

These results are sufficient to show that when using radium or roentgen rays in bone cases, careful thought should be given to the dosage, and the danger of overradiation should be appreciated. At a recent conference at the Memorial Hospital, one of the visitors in discussing these cases stated that we should not be concerned if we did devitalize or destroy a large portion of the long bones (tibia or femur) because we can then amputate, and that preoperative radiation would prove an important factor in preventing metastases. As we have already stated, we believe that at present there is not the slightest evidence in support of this view. We have no evidence that radium or roentgen rays, even when carried to the point of devitalizing the bone, has ever succeeded in entirely destroying a primary osteogenic sarcoma of the bone, much less prevented its metastasizing. If no metastases have occurred at the time of the amputation, caused by the escape of tumor cells in the lungs or elsewhere, we can see no advantage in preliminary radiation. If some of these tumor cells have escaped before radium treatment is started, then no amount of prolonged radiation of the tumor of the long bone will have material effect on metastases already present.

PREOPERATIVE IRRADIATION IN BONE SARCOMA

We have never been convinced of the wisdom or value of radium or roentgen rays as a preoperative measure in any type of cancer, and we believe that at present there is no definite evidence of the value of either agent as such a measure. While preoperative radiation has been strongly advocated by many roentgenologists, and a number of surgeons have adopted it as a routine measure, Greenough [13] of Boston in a paper read before the American Cancer Research Society in 1923 stated that there is no proof of its value in cancer of the breast and that it was attended by certain distinct disadvantages in the way of delayed wound healing. Also, Wood [14] of New York has come out strongly against preoperative radiation in cancer in general. Lee [15] believes that preoperative radia-

11. Coley, W. B.: Prognosis in Giant Cell Sarcoma of the Long Bones, Ann. Surg. **79**:321 (March); 561 (April) 1924.

12. Bancroft: S. Clin. N. Amer. **1**:1739 (Dec.) 1921.

13. Greenough: Cancer of Breast, Tr. Am. Cancer Research Society, 1923.

14. Wood, F. C.: S. Clin. N. Am. **5**:263 (Feb.) 1925.

15. Lee, B. J., and Herendeen, R. E.: Ann. Surg. **82**:404 (Sept.) 1925.

tion is of distinct advantage in cancer of the breast. We believe that the question is still subjudice as regards malignant tumors in general, but in the special field of long bone sarcoma in the cases in which it has been definitely decided that early amputation offers the greatest hope of saving the life of the patient, we can see no advantage in preoperative radiation. In these cases the use of this measure can be justified only on the ground that the action of radium or roentgen rays on the tumor cells produces certain changes in the body fluids which may have an inhibitory action on the tumor cells that have already escaped from the primary tumor through the circulation or lymphatics and have been carried to other parts of the body, later giving rise to metastatic tumors. Such action is not yet proved. In a number of our cases the evidence certainly points to the possibility of metastases being directly brought about by heavy radiation, and we can see no ground for taking the risk of such a result, especially in cases in which from the start we believe there is no reasonable hope of controlling the disease or of saving the limb by radiation. In these cases, it would seem far wiser to perform an immediate amputation following this with prophylactic toxin treatment supplemented by roentgen-ray treatment over the chest.

We are aware that some observers, in fact, two of our own colleagues at the Memorial Hospital, believe that preliminary radium or roentgen-ray treatment may be of decided value in long bone sarcoma even if the case goes on to amputation. This belief is based on the theory that certain changes may be produced by the roentgen rays or radium that may lessen the chances of metastases after amputation. Whatever may be the theoretical grounds for this belief, it is evident that the question can be settled only by actual experience, and fortunately we now have a sufficiently large number of cases treated by preliminary radiation followed by amputation to permit some definite conclusions (for example, case 109 in table 7).

We have a group of twenty-four cases in which either the roentgen ray or radium was used for varying periods and amputation then performed after failure to control the disease by radiation; of these sixteen are dead and two others have pulmonary metastases. Only one of these patients has remained well for more than three years; the remaining cases are too recent to enable one to draw any deductions as to the final outcome.

We have another group of twenty-seven operable cases of osteogenic sarcoma in which roentgen rays or radium was given as a primary method of treatment in preference to early amputation, in which either metastases developed or the condition became inoperable during the course of treatment. If we compare this group of cases with a similar group treated with toxins alone or toxins and radium after amputation we find a striking contrast. These last two groups were practically

identical as regards the pathologic or histologic type of tumor, so that it is quite fair to compare the results of the different methods of treatment.

In spite of our results at the Memorial Hospital, and in spite of the uniformly poor results of other men, we have continued using roentgen rays and radium year after year, in the hope that further experience and increased knowledge as to the best method of applying these agents might result in a cure of this baffling disease. The time has now come, we believe, to pause and reconsider the problem. It might be well to ask ourselves if we are any longer justified in advising a patient with an operable periosteal or osteogenic sarcoma of the long bones to undergo a course of radium or roentgen-ray treatment as a primary measure before amputating, at least without telling him frankly that we can offer no hope of saving his limb, and that later amputation offers little hope of saving his life. If the tumor is of the round cell variety (endothelioma, according to Ewing) in the operable stage or spindle cell with little new bone formation, we could tell the patient that there is a small chance of saving his limb by a combination of toxins and radium treatment, but that if marked improvement is not noted in a few weeks, amputation should be performed, followed by prophylactic toxin treatment, and that this measure offers a practically even chance of saving his life. If the patient prefers to lose his life rather than his limb, then, and then only, are we justified in the use of prolonged radiation alone in the osteogenic type.

The following question naturally arises: Have we as yet sufficient evidence as to what can be accomplished by radium and roentgen rays in osteogenic sarcoma to enable us to decide whether radiation should be the method of choice in early primary cases? While the question cannot be regarded as definitely answered, it would seem that our own failure to produce a single cure of undoubted osteogenic sarcoma in which the diagnosis was established by microscopic examination, and the fact that the observations of distinguished radiologists here and abroad are in entire accord with our own, justifies us in reconsidering the whole question. Regaud, director of the Radium Institute of Paris, Forschell of Stockholm, Pinch, director of the Radium Institute of London, and Burnham of Baltimore, all agree that bone sarcoma is exceedingly resistant to roentgen-ray or radium treatment, and no one has reported a cure in osteogenic sarcoma. In his annual report for 1921, Pinch stated:

> It is to be noted that radium treatment is useless in all cases of disease affecting actual bone substance, whether malignant or nonmalignant. It has been tried in such widely diverse conditions as rodent ulcer affecting the cranial bones, osteosarcoma, myositis ossificans, osteitis deformans and ivory exostosis, and in no instance has the least benefit ever been recorded.

We believe that our own results further warrant us in abandoning radiation as a routine method of treatment in early primary osteogenic sarcoma, and substituting early amputation followed by prolonged toxin treatment systemically, and postoperative radiation to the lungs.

Dr. Pinch has stated:

> In my experience, radium is useless in cases of endosteal sarcomas of the osteogenetic type, and I have never succeeded in effecting the slightest improvement in this class of disease.

AMPUTATION

A fairly accurate idea of the curative value of radical operation alone (amputation or extirpation) in sarcoma of the long bones may be obtained from a study of the statistics of the Tubingen Clinic (Professor von Bruns) reported by O. Kocher; these statistics have already been quoted in full in our earlier papers on the subject. The latest and most authoritative statistics showing the results of radical operation alone in sarcoma of the long bones may be found in an article by Escher [16] covering sixty-three cases treated at the von Eiselberg Clinic, Vienna, from 1901 to 1918. Of this series twenty-one patients died of metastases, and nineteen without metastases, within one year of the operation; thirteen were of periosteal origin and twenty-three were myelogenous; only six of the sixty-three patients were reported well beyond a two-year period. In twelve cases resection was performed, and in the remainder, amputation. Among the cases apparently cured by amputation were: (1) a chondrosarcoma of the tibia of five years' duration before amputation, well eight and one-half years; (2) a chondrosarcoma of the femur of four years' duration, well eight years after hip joint amputation; (3) a periosteal round cell sarcoma of the lower end of the humerus, well eighteen years after amputation at the shoulder joint.

Escher discusses the various methods of conservative treatment only to discard them all, and places himself on record as being in favor of nothing less than immediate radical amputation, a resection, in both the periosteal and myelogenous types of sarcoma of the long bones. He adds that, in spite of the great progress in roentgen-ray therapy, such treatment does not result in an actual cure in cases of bone sarcoma, although it may be of great value in inoperable cases. Resection he regards of value only in the early stages in which the tumor is undoubtedly encapsulated. A striking fact brought out by the statistics of these two clinics is that the malignancy of the central or myelogenous group of sarcomas very nearly equalled that of the periosteal, and this is true of Kocher's series.

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16. Escher: Arch. f. klin. Chir. **114**:553, 1920.

Our own series of cases show that amputation alone, even when performed at an early stage of the disease, rarely results in a cure. A recurrence or metastasis has taken place within from a few months to a year in 98 per cent of the cases. We have no patient treated by amputation alone, without preoperative toxin or radium treatment, who has remained alive and well for a period of three years. Our series show only twelve patients treated by amputation alone, with no cures. According to Bloodgood, only two out of his seventy patients with periosteal sarcoma treated by amputation survived the three year period.

At a symposium on long bone sarcoma held during the meeting of the American College of Surgeons in Philadelphia in 1922, Meyerding of the Mayo Clinic reported the end-results in 100 cases of sarcoma of the long bones treated at the Mayo Clinic since 1910 (with complete roentgen-ray, clinical and pathologic data). In many of these cases, amputation had been performed, followed by a routine course of toxin treatment, in some cases supplemented by roentgen rays. A careful follow-up showed 50 per cent of the patients still alive, 16 per cent well over five years. In striking contrast to this was the report of Besley of Chicago, who took part in the discussion at the same meeting. He stated that of fifty-six cases of sarcoma of the long bones treated by amputation at the Cook County Hospital, in which no prophylactic treatment had been given, not a single patient operated on prior to September, 1920, was known to be alive at the time of his report, irrespective of the pathology of the tumor.

Thus far the periosteal cases have been grouped without regard to the histologic type. While the end-result is death in practically all the cases regardless of the type of cell, the duration of life varies considerably in the different histologic types. In the round cell variety, classified by Ewing as endothelioma, death often occurs within from six months to one year, while in the sclerosing or osteoid type the duration of life may be two years or more. The duration of the disease is likewise materially altered by the method of treatment employed. In many cases the disease has been held in check for months, and in some cases for two or three years, by roentgen rays or radium; unfortunately, however, these cases have gone on to a fatal issue. As a rule, the cases in which there is little or no new bone formation (round cell sarcoma or endothelioma) show the greatest effect from both roentgen rays and radium, in some cases amounting to practically complete disappearance of the tumor as far as clinical and roentgen-ray evidence goes; yet in nearly all of these cases recurrence of metastases develops, usually within from a few months to a year. The cases characterized by marked new bone formation—the ordinary type of osteogenic sarcoma—show extreme resistance to roentgen rays, radium or toxins, and while some temporary improvement is often observed, it is usually only of short duration. In a number

of these cases, metastases have developed during the early stages of roentgen-ray or radium treatment, whether favored by the rapid breaking down of the tumor, thus permitting living cells to be carried to remote parts of the body, or merely as a coincidence, it is impossible to say. We have observed a number of cases that would seem to suggest the possibility of metastases having been caused or hastened by treatment.

Whether this is true or not, the fact remains that no patient with this type, that is, with marked new bone formation, has been cured by roentgen rays or radium or toxins. Therefore, we can see no reason why any of these methods of treatment should be employed in this type of tumor unless it can be shown that no other treatment offers any greater hope of saving the life of the patient. This brings us to a consideration of the other alternative: amputation followed by prolonged treatment with the mixed toxins of erysipelas and *Bacillus prodigiosus*. Fortunately, we have a fairly large group of cases including many of the type just mentioned that have been treated by amputation followed by the use of the toxins. Of the group of forty-one cases so treated, twenty, or 49 per cent, have remained well from three to eighteen years. In three of these cases the toxins were given for less than two weeks, too short a period in which to expect much benefit. The importance of these results is at once apparent when we compare them with the smaller group of patients treated by amputation alone (no cures) or amputation after prolonged radiation (only one patient, well three years). If amputation had been performed earlier in many of these cases and had been followed by toxins, we believe that an even larger number than 50 per cent might have been saved.

In view of these results, we feel justified in urging immediate primary amputation in all cases of osteogenic sarcoma associated with a large amount of new bone formation, to be followed by prolonged toxin treatment. Conservative treatment of any kind is not justified in this group of cases for the reason that the time intervening, necessary for carrying out the conservative treatment, materially increases the chances for the development of metastases, whether or not such development is favored by the action of the treatment. If there were any hope of a cure of the patient by such treatment, there might be some justification for attempting to save the limb, but thus far we have no evidence encouraging us in this hope.

INOPERABLE CASES

It has been found possible to save the life as well as the limb in a limited number of inoperable cases, in which the disease had advanced too far for amputation at the time of first observation. These cases are of sufficient interest to warrant a brief reference: We have ten cases

(cases 3, 4, 15, 19, 21 and 22) in which the disease had advanced beyond any hope of relief from surgical measures which have been successfully treated, and the patients have remained alive and well from two to twenty-four years. In at least one case, definite lung metastases were present at the time the treatment was begun, and in four other cases there was evidence of probable metastases. A further study of these cases shows that none was of the periosteal osteogenic type with a large amount of new bone formation, but rather of the round cell sarcoma type, or, according to Ewing's recent classification, endothelioma, a type that has been found to respond much more rapidly to toxins, roentgen rays and radium than the osteogenic type.

In one case, an extensive sarcoma of the tibia with metastases in the inguinal and iliac glands, the tumor was pronounced osteogenic sarcoma by Ewing, but the roentgenogram showed no marked new bone formation. This patient recovered under radium and prolonged toxin treatment, his limb was saved, and he is in good health, nine years later.

ENDOTHELIOMA

Of the twenty-six patients with endothelioma, as well as round cell sarcoma without new bone formation, included in this series of cases, thirteen are alive and well from three to fifteen years. It is interesting to note the method of treatment employed in these living patients:

1. Tibia; radium for from two to three years followed by amputation; well, one and one-half years; Ewing's diagnosis.

2. Femur; amputation for sarcoma of femur; was then treated with toxins and radium for multiple metastases in skull; well six years later; Ewing's diagnosis.

3. Fibula; amputation; multiple metastases developed in groin, iliac fossa and lungs; treated with toxins and radium; patient well five years later; Ewing's diagnosis.

4. Femur, extensive involvement; amputation followed by toxins; patient well fifteen years later; Ewing's diagnosis.

5. Femur; extensive metastases to pectoral region and ilium; roentgen-ray treatment to femur; metastases of ilium treated with toxins alone; patient well ten years later; diagnosis by Dr. E. K. Dunham, professor of pathology, Bellevue Hospital Medical College.

6. Femur; diagnosis from clinical and roentgen-ray evidence and macroscopic examination on exploratory operation; treated with toxins alone; limb saved; patient well ten years later.

7. Femur; inoperable; clinical and roentgen-ray diagnosis; treated with toxins and radium; patient well seven years later.

8. Tibia; amputation followed by toxins; patient well seven years later; microscopic diagnosis confirmed by Ewing.

9. Clavicle; treated with radium alone; patient well three years later; died, July, 1925, cause of death unknown; no local recurrence; Ewing's diagnosis.

10. Clavicle; excision followed by toxins; patient well fifteen and one-half years later; Ewing's diagnosis.

11. Tibia; clinical and roentgen-ray diagnosis; treated with toxins and radium; limb saved; patient well five years later.

12. Femur; treated with toxins and radium; limb saved; patient well five years later.

13. Clavicle; clinical and microscopic diagnosis; round cell sarcoma; excision followed by toxins; patient well seventeen years later; diagnosis by Dr. W. F. Whitney, Harvard Medical School.

In September, 1905, Howard and Crile [17] of Cleveland published an important article on endothelial bone tumors containing a report of nineteen cases found in the literature in addition to four cases that had come under their personal observation. The locality of the tumor in the nineteen cases was: the humerus in seven, the tibia in three, the femur in eight, and the ulna in one case. In the majority of these cases the origin of the tumor was apparently in the central portion of the bone from which it spread along the narrow cavity and later involved the entire bone. The tumors were quite vascular and, in several cases, were mistaken for bone aneurysm. In 63 or 64 per cent metastases were observed. We find few references in the medical literature to endothelioma of the bone until Ewing [18] in 1921 reported a most interesting case which he classified as endothelial myeloma and which probably belonged to the same group of tumors. Since that time there have been observed at the Memorial Hospital sixteen cases of malignant tumors of the long bones, practically all of which occurred in the shaft of the bone, which have been classified by Ewing as endothelioma or endothelial myeloma. While most of these tumors are still classified by the majority of pathologists as round cell sarcoma, and while there may be good reasons for hesitating to accept the view that they are of endothelial origin, we must admit that they do form a fairly definite clinical and pathologic group and differ materially from the ordinary type of osteogenic sarcoma. Furthermore, they differ quite as much in their response to treatment with radium, roentgen rays or toxins.

The clinical features of a typical case are somewhat as follows: The trouble usually originates in the shaft of a long bone instead of in the neighborhood of one of the ends of the bone, which is usually the case in osteogenic sarcoma. There is a history of antecedent local trauma in about the same proportion of cases as in the ordinary type of sarcoma. The tumor is apt to involve a considerable portion of the bone, one half to one third of the shaft, at the time of first observation. While the trouble usually starts in the central portion of the bone, there are cases

17. Howard and Crile: Ann. Surg., September, 1905.

18. Ewing, James: Rep. New York Path. Soc., 1921.

in which it apparently originates in the periosteum or subperiosteal tissue. It seldom destroys sufficient bone to cause a pathologic fracture, although pathologic fracture has been observed in several of our own cases. It shows little or no tendency to produce new bone, and in these cases one never sees the marked new bone production with typical lines radiating at right angles to the shaft of the bone. It has more of a tendency to produce separate layers of tumor tissue laid down parallel to the shaft of the bone. In our own series of cases, the tumors have not as a rule proved to be so highly vascular as has been found by Howard and Crile. One of our most recent cases was highly vascular. In contradistinction to the ordinary osteogenic sarcoma these tumors show marked susceptibility to the influence of roentgen rays, radium and toxins, often disappearing entirely after a few weeks' treatment; unfortunately, however, the disease is apt to recur within a few months either locally or in the form of metastases to the lungs or other bones. This type of tumor shows a special predilection to invade other bones, especially the skull.

These cases have been generally described as round cell sarcoma by most pathologists. They resemble round cell sarcoma in that they are composed of diffusely growing cells with round nuclei. Ewing states that three anatomic forms may be recognized: (1) multiple endothelioma; (2) solitary angio-endothelioma and (3) diffuse endothelioma. Ewing cites Marckwald's case of multiple endothelioma in which nearly every bone in the body was the seat of small medullary tumors; he states that this is the only recorded case of its kind, although Symmers and Vance [19] describe a somewhat similar one. While in several of the cases compiled by Howard and Crile multiple tumors were observed, these were regarded as secondary. These authors state that this type of tumor is more prone to produce metastases than any other, 66 per cent of their cases having metastasized. Whether the tumors in this group were primary or secondary and metastatic from one original growth, Ewing believes it is impossible to determine. A study of our own cases strongly supports the opinion that the multiple tumors that practically always develop a considerable period of time after the original tumor are really metastatic. He states: "The structure consists of endothelial-like cells in small groups or sheets, often forming alveoli and sometimes cysts containing serous or mucinous fluid."

ANGIO-ENDOTHELIOMA

According to Ewing, this form "usually appears as a single tumor which sharply and completely destroys the bone and often reaches large dimensions. Its expansile pulsation places it among the malignant bone aneurysms. The roentgen ray shows a clean cut destruction of bone by

19. Symmers and Vance: Am. J. M. Sc. **152**:28 (July) 1916.

a central tumor which displaces and eventually invades the soft parts. There is no bony capsule and the periosteum is free. This disease returns after amputation and produces metastases. It grows much more rapidly than the benign central giant cell tumor, but can hardly be distinguished from telangiectatic sarcoma on clinical and roentgen-ray evidence. From the ordinary osteogenic sarcoma it differs in that it fails to show a wide zone of involved periosteum extending beyond the main tumor mass. These differences are rendered obvious by a comparison of the photographs of gross specimens with roentgenograms. The structure is highly characteristic, consisting of large clear endothelial cells in cords and columns inclosing circulating blood. The subjects are chiefly adults."

We have only two examples of this type, one referred to us by Dr. C. F. Ball of Rutland, Vt., who presented the Memorial Hospital with the specimen and roentgenograms. Ball's case occurred in a man. Following an injury to the shoulder, a tumor appeared and developed rather rapidly. When the case was presented at the Memorial Hospital staff conference, it was found impossible to make a diagnosis from the roentgenogram and the clinical history. The opinion of the majority of the staff was that it was a giant cell sarcoma. Ball presented the specimen from recent amputation. The gross pathology and macroscopic appearance so strongly resembled giant cell sarcoma that Ewing believed it to be such. The microscopic examination, however, showed it to be an angio-endothelioma. The patient is still living, one year later.

SOLITARY DIFFUSE ENDOTHELIOMA

Ewing states that "the great majority of endotheliomata of bone belong to this group. They occur usually in the shaft of the long bones instead of near the end as may often be the case in angio-endothelioma. They involve a large portion of the shaft. The enlargement of the bone is due to the formation of concentric layers so that the roentgen-ray picture often shows the laminated structure. There is little or no new bone formation in this type of tumor. Although there is much bone absorption, pathologic fracture occasionally occurs but with much less frequency than in the giant cell or angio-endothelioma tumors. The bone assumes a fusiform appearance often involving almost the entire shaft" (case 48).

Metastasis in lymph nodes is more common in this type of tumor than in osteogenic sarcoma, and we believe that this type is more prone to metastasize in other bones than is the ordinary type of osteogenic sarcoma. In our series, the cases 4, 21, 48 and 49 have shown metastases in bones.

DIFFERENTIAL DIAGNOSIS

Endothelioma differs from myositis ossificans in that in the former condition, the tumor is softer in consistency; it involves the entire circumference of the bone; as a rule it invades a much more extensive portion of the bone; it is smooth and has no irregularity such as is felt in myositis ossificans. The roentgen ray makes it possible in most cases definitely to distinguish the two conditions; the periosteal line is intact in myositis ossificans whereas it is irregular and indented or lost in endothelioma. There is no bony destruction in myositis ossificans as in endothelioma, but there is new bone production. Endothelioma is easily differentiated from giant cell tumor by its usual location, i. e., in the shaft of the bone. Bloodgood has estimated that only 1 per cent of giant cell tumors occur in the shaft of the long bones.

In one of our cases, an ulna (case 97 in table 7), several expert roentgenologists had made a diagnosis of syphilitic osteomyelitis; our clinical diagnosis was sarcoma. In view of the doubt expressed after both clinical and roentgenologic examinations, we decided to do an exploratory operation. The section was examined by Ewing, who pronounced it an endothelioma. A roentgenogram of this patient was published by Ewing.[20] The patient proved extremely susceptible to combined treatment of radium and toxins, and the tumor apparently entirely disappeared within two or three months. Unfortunately, it soon recurred and showed little effect from like treatment; a few months later, metastases developed in the liver, probably also in the lungs, and proved fatal. The entire course of the disease in this case was seventeen months.

The first case observed at the Memorial Hospital and the one that called Ewing's attention to this interesting group of cases was case 163 in table 7. This case has been fully described by him.[18] The roentgenogram clearly simulated the ulna case, already cited, in general appearance, but the tumor was more bulky. The case showed great susceptibility to radium alone (the patient had received eight doses of toxin before coming to the hospital), and the tumor apparently entirely disappeared under heavy radiation. Four months later the tumor recurred locally and in the skull, causing death. The whole course of the disease in this case was seventeen months.

In a paper read before the New York Surgical Society one of us[21] reported a case believed to be a periosteal sarcoma of the femur (case 11). We now believe that this case should have been classified as a diffuse endothelioma.

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20. Ewing, James: Bone Sarcoma, Arch. Surg. 4:491 (May) 1922, fig. 3.

21. A full report of this case was published in Ann. Surg., July, 1913.

The question of the best method of treatment of this type of tumor primary in a long bone is still a difficult one. While Ewing in his publication of 1922 pointed out the fact that these tumors were remarkably susceptible to roentgen rays and radium and that, therefore, amputation was probably unnecessary, up to that time he was unable to report a single cure of this type by radiation and stated that "it does not appear that any cases have been treated by modern roentgen-ray technique." He believes the diagnosis can generally be made on the clinical history, the peculiar roentgenogram, and the early response to radium. He adds, however, that competent observers have firmly maintained that some of his cases were osteomyelitis. Since 1922 there have come under our observation three other cases in which the clinical and roentgen-ray evidence, as well as the microscopic examination following exploration, all pointed to a diagnosis of osteomyelitis, and yet the subsequent history proved them to be endothelial type sarcoma. We ourselves feel that the advantages to be gained by an early diagnosis in doubtful cases greatly outweigh the disadvantages of exploratory operation.

TABLE 3.—*Age of Patients in Endothelioma Group*

	Patients
Up to and including 5 years	2
6 to 10 years	6
11 to 20 years	7
21 to 30 years	5
31 to 40 years	5
41 to 50 years	1
Sex: 17 males, 9 females.	26

Since Ewing's paper was written (1922) we have had an opportunity of studying a number of additional cases, making at present a total of twenty-six cases. While this further study has confirmed all that he said about the striking susceptibility of these tumors to roentgen rays and radium, so far we have not succeeded in curing a single case by either of these agents alone. On the other hand, we have succeeded in causing the total disappearance of the tumors in two far advanced cases with multiple metastases (in the skull in one case, and in the inguinal and iliac glands and lungs in the other), and both patients are now in good health, more than five years later, following combined treatment with toxins and radium. These cases are so remarkable that they are given in detail. In another far advanced case the disease was apparently controlled and the patient remained well for nearly two years, when she developed metastases in the abdomen and brain, which proved fatal. If to these cases we add the two previously mentioned, occurring in the early series before the condition was recognized, we have two more patients cured and well more than ten years, treated by toxins and

roentgen rays in one case and toxins alone in the other. The limb was saved in both cases and the patients are well at the present time.

Our own observations force us to believe that the cases that begin with mutiple primary tumors must be very rare. We have never observed such a case and we are inclined to regard the subsequent development of multiple tumors as merely a generalization of the disease from a single primary focus.

From a study of our own series of cases, which represented different degrees of malignancy—in certain cases the disease ran a rapid course, killing the patient in a few months, and in other cases, the disease continued for one or two years before proving fatal—we have not found it possible to determine definitely the degree of malignancy by the histologic structure of the tumor.

In regard to the first group mentioned by Ewing, i. e., encapsulated extraperiosteal fibrosarcoma, while these tumors may be less malignant than those mentioned in the other groups, they are extremely rare, and we found only one case of this type in our series. This patient was treated first by local exploratory operation, and later by radium and roentgen rays; at the end of the third year, a pathologic fracture occurred; an amputation was performed one year ago; the patient was well, January, 1926, nearly two years after operation. On the other hand, we have examples of subperiosteal sarcoma diagnosed as fibrosarcoma, in which the disease ran a rapid course, causing death within six or eight months.

There is another group of cases in which surgical opinion varies considerably in regard to the prognosis; this is the so-called chondrosarcoma or osteochondrosarcoma in which there is considerable cartilage in the tumor. Many have regarded these cases as less malignant in that they run a slower course. A study of our own series, as well as the cases reported in the literature, shows that many of these cases run a comparatively rapid course, and that few if any are cured by amputation alone.

There is a rare type of sarcoma designated by Gross as chondro-osteoid sarcoma, and often called the sclerosing type of sarcoma, in which the prognosis as to duration of life is better than in the more cellular types. Practically all of these cases end in death after amputation alone. In some cases the disease may last a number of years, four or five or more, and yet in cases of long duration there is always the possibility that the original trouble may have been a traumatic productive osteitis or myositis ossificans which later on underwent malignant degeneration such as we frequently see in tumors of the soft parts, for example, carcinoma of the breast originating in a chronic mastitis. As a rule the *more highly cellular* the structure of the tumor, the more rapid the growth with the greater probability of early metastases. On the other hand, we have seen a typical fibrosarcoma of the soft parts, so slightly cellular that the pathologist thought it might well be called a fibroma,

develop with great rapidity and cause death from metastases within six months. In one of our bone cases, a tumor of the humerus with extensive involvement of the midshaft, a biopsy was made and Ewing's diagnosis was fibrochondroma of slight malignancy. Several radium treatments were given with little effect; one of us later did an amputation at the shoulder joint, following this by a brief course of prophylactic toxin treatment; metastases developed in four months, causing death a few months later.

These cases show that it is not always possible to determine the degree of malignancy of a tumor of the long bones by the histologic structure.

We believe that our results warrant us in using radium or roentgen rays, preferably the former, in most cases of diffuse endothelioma or round cell sarcoma associated with little or no new bone formation. We believe that by combining toxins with radium in these cases better results are obtained. The fact that we have been able fully to control the disease in several far advanced cases of this type which had already metastasized by the combined treatment with radium and toxins justifies us in the hope that similar treatment in early operable cases may result in saving the limb as well as the life of the patient.

We believe that the use of radium or roentgen rays is still justified in cases of early operable giant cell sarcoma and that it will prove curative in a certain number of cases. That it will prove superior to curettage alone, or curettage followed by toxin and radium treatment (our own choice) is still a matter of grave doubt. It is important to note that our present series of cases shows that the period of treatment with radium or roentgen rays is often greatly prolonged, in some cases over one or two years; that recurrences are not infrequently noted, and that the period of disability is likely to be considerably greater than when surgery-curettage-toxins is the method of choice.

RESULTS OF ROENTGEN RAY AND RADIUM TREATMENT IN PRESENT SERIES OF CASES

Of sixty-seven operable cases of periosteal sarcoma of the long bones, including endothelioma, in which roentgen rays or radium was the primary method of treatment, thirty-six patients are known to have died. As regards the seventeen living patients, in ten amputation or resection was performed and in addition the roentgen ray or radium was used. In the remaining seven living patients, the diagnosis was confirmed by microscopic examination in only one case (sarcoma of clavicle) and in the others in only one case was the clinical and roentgen-ray evidence sufficiently clear to establish the diagnosis beyond reasonable doubt.

A brief résumé of the less recent living cases is as follows:

Case 33; sarcoma of femur; disease was held in check for three years; pathologic fracture occurred; amputation performed; patient well nearly two years later.

Case 13; sarcoma of humerus; roentgen-ray treatment; resection; patient well seven years later.

TABLE 4.—*Primary Operable Cases of Periosteal Osteogenic Sarcoma, Endothelioma and Malignant Central Sarcoma Treated Primarily with Roentgen Rays and Radium, and Later by Amputation After Failure to Control Disease*

Case	Locality	Treatment	Results
1	Ulna	Radium four months; amputation	Death; metastases six months
2	Humerus	Radium six months; amputation	Death; metastases five months
3	Femur	Radium	Death
4	Femur	Radium and roentgen rays, 1919; disease controlled four years; pathologic fracture, necessitating amputation	Patient well one year
5	Femur	Radium and high voltage roentgen rays one year; partial control; amputation	Patient well two years
6	Humerus, periosteal not osteogenic	Radium four months; disease not controlled; amputation	Patient well three years
7	Tibia, central, giant and spindle cell	Radium; amputation	Death
8	Tibia	Curettage; radium; recurrence; amputation	Death; metastases four months
9	Tibia, central, giant cell	Curettage; radium; recurrence; amputation; recurrence	Death
10	Scapula	Radium (tumor disappeared) recurrence; amputation	Death
11	Tibia, central, giant cell, angioendothelioma (?)	Roentgen rays; amputation	Well one and three-fourths years
12	Femur	Radium; amputation	Death; metastases
13	Humerus	Roentgen rays; amputation	Death; metastases
14	Humerus	Roentgen rays; amputation	Well two years plus
15	Tibia	Roentgen rays; amputation	Death; metastases
16	Tibia; endothelioma	Radium two years; amputation	Well one and one-fourth years
17	Femur; central, giant cell (clinical and roentgen-ray diagnosis)	Radium and roentgen rays; amputation	Death; metastases
18	Femur	Roentgen rays two and one-half months; amputation	Death; metastases
19	Femur	Roentgen rays six weeks; amputation	Death; metastases
20	Tibia	Roentgen rays; amputation	Death; metastases
21	Humerus	Radium; amputation	Death; metastases
22	Femur	Radium; amputation	Death; metastases
23	Tibia	Roentgen rays; amputation	Death; metastases
24	Os calcis	Roentgen rays; amputation	Death; metastases
25	Tibia	Roentgen rays; amputation	Death; metastases
26	Femur	Roentgen rays six weeks; amputation; toxins six months	Well two years
27	Tibia	Roentgen rays six weeks; amputation	Death; metastases four months
28	Tibia	Roentgen rays four months; amputation	Recent case
29	Femur	Roentgen rays; amputation	Metastases

Case 28; sarcoma of lower end of humerus; radium treatment for four months; disease not controlled; amputation performed; patient was reported well nearly three years later, but no medical examination was made.

Sarcoma of humerus; resection followed by prophylactic radium treatment; patient well five years later.

Case 12; tumor of femur; roentgen-ray diagnosis; periosteal sarcoma (no microscopic examination); clinical history suggested possibility of myositis ossificans; treated with roentgen rays and radium; well three and one-half years.

Case 34; sarcoma of femur; clinical and roentgen-ray diagnosis (no microscopic examination); treated with roentgen rays; well two and one-half years later.

Sarcoma of clavicle involving the cervical spine; microscopic diagnosis: endothelial myeloma; treated with radium alone; patient in good health for four years; died after a week's illness in June, 1925; cause of death not definitely known.

TABLE 5.—*Operable Cases of Periosteal Osteogenic Sarcoma or Endothelioma Treated Primarily with Roentgen Rays or Radium, which Became Inoperable or Developed Lung Metastases During Treatment*

1	Clavicle
2	Humerus
3	Humerus
4	Femur
5	Humerus
6	Tibia
7	Femur
8	Femur
9	Radius
10	Femur
11	Femur
12	Femur
13	Femur
14	Femur
15	Os calcis
16	Humerus
17	Femur
18	Humerus (Bellevue Hospital)
19	Tibia
20	Tibia
Cases in Which Treatment Was Carried Out at Other Hospitals and in Which Patient Was in an Inoperable Condition on Admission to Memorial Hospital *	
21	Humerus
22	Femur
23	Humerus
24	Humerus
25	Clavicle

* In several cases in this group, metastases developed soon after the beginning of heavy treatment with high voltage roentgen rays or radium, thus raising the question of whether the too rapid breaking down of a vascular sarcoma by radiation may not cause some of the living cells to be carried to different parts of the body, particularly the lungs, thus producing metastases earlier than otherwise would have occurred.

In twenty-seven patients treated primarily with roentgen rays or radium, the condition became inoperable before amputation was advised or before the patient had consented to it. In twenty-nine cases, amputation was performed after failure to control the disease by radiation; twenty-one of these patients died, and eight are living. In three of the living patients, the mixed toxins were used as a prophylactic after operation; one patient is well nearly two years, another is well a little over one year, and the other case is recent.

In sixteen cases amputation was performed without the use of previous treatment (toxins, roentgen rays or radium) and without any prophylactic after-treatment. In all of these cases death occurred, in the majority about a year after amputation. In one case metastases of the

lungs developed seven years after amputation, and in another, metastases of the skull five years after amputation.

In twenty-four cases preoperative roentgen-ray or radium treatment had been given but no prophylactic after-treatment of any kind. Of this group fifteen died, and of the remaining nine living patients only one has reached the three year period (this patient was indirectly reported as being well, but no physical examination was made).

It is interesting to compare the foregoing results with those obtained in table 6.

TABLE 6.—*Patients Treated by Amputation Followed by Toxins**

Case	Locality	Result	Remarks
24	Tibia	Well 4 years	Diagnosis confirmed by Ewing
22	Fibula	Well 4½ years	Diagnosis confirmed by Ewing
8	Femur	Well 15 years	Diagnosis confirmed by Ewing
17	Femur	Well 8 years	Diagnosis confirmed by Ewing
10	Femur	Well 19 years	Diagnosis confirmed by Ewing
31 (in table 7)	Femur	Well 10 years	Diagnosis confirmed by Ewing
5	Femur	Well 18 years	Diagnosis confirmed by Sondern
26	Femur	Well 5 years	Diagnosis confirmed by Ewing
21	Femur	Well 6 years	Diagnosis confirmed by Ewing
3	Metatarsal bone	Well 28 years	Diagnosis confirmed by New York Hospital Laboratory
16	Femur	Well 8 years	Diagnosis confirmed by Ewing
12	Radius	Well 12 years	Diagnosis confirmed by Ewing
20	Tibia	Well 7½ years	Diagnosis confirmed by Ewing
14	Metatarsal bone	Well 10 years	Diagnosis confirmed by Ewing
18	Femur	Well 8½ years	Diagnosis confirmed by Ewing
	Humerus	Well 8 years	Diagnosis confirmed by Ewing
11	Ulna	Well 15 years	Diagnosis confirmed by Whitney (Harvard Medical School)
6	Femur	Well 16½ years	Diagnosis confirmed by Ewing
	Clavicle	Well 15 years	Diagnosis confirmed by Ewing
	Clavicle	Well 15 years	Diagnosis confirmed by Whitney

* Of forty-one patients treated by amputation followed by prophylactic toxins (thirty-nine patients being treated prior to three years ago) the twenty given here are alive and well from three to twenty-eight years.

RESULTS IN CASES TREATED WITH TOXINS ALONE OR COMBINED WITH SURGERY

Of forty-eight patients treated with toxins alone or toxins combined with surgery, twenty-two are alive and well beyond the three year period; in all of these cases the diagnosis was confirmed by microscopic examination; in three additional living patients (in whom the limb was saved) the diagnosis was based on clinical roentgen-ray evidence, but this was sufficiently clear so as to leave little doubt as to the correctness of the diagnosis. In thirty-eight cases of the periosteal type, nineteen of the patients were well from three to eighteen years.

LIVING PATIENTS

Of eighty-eight patients with operable cases of periosteal osteogenic sarcoma of the long bones, including endothelioma, treated with toxins alone, toxins and radium, or amputation and toxins, forty-seven, or 53.3 per cent, are living; thirty-eight are alive and well from three to

TABLE 7.—*Group 1: Patients Treated by Toxins or*

Case	Date	Age	Sex*	Locality	Trauma	Clinical Diagnosis	Roentgen-Ray Diagnosis
1	January, 1907	12	♂	Femur, lower end	Kicked above knee; tumor 1 week later	Periosteal sarcoma	Periosteal sarcoma
2	September, 1912	27	♀	Femur shaft, middle two-thirds	None.....	Periosteal sarcoma	Periosteal sarcoma
3	April, 1897	26	♀	Femur, lower end	Dislocated knee cap and wrenched knee 2 years before	Periosteal sarcoma	Periosteal sarcoma
4	April, 1909 Williamson's case	Adult	♂	Femur, lower end	?.....	Periosteal sarcoma, unoperable (Dr. W. J. Mayo)	Periosteal sarcoma
5	June, 1899	41	♂	Femur, upper end	None.....	Sarcoma.....	None.....
6	1915	20	♂	Femur, lower end	Yes; local fracture	Periosteal sarcoma	Periosteal sarcoma
7	March, 1920	19	♂	Femur, lower end	Fall 3 months before	Sarcoma.....	Sarcoma.....
8	1911	21	♀	Femur, lower end	None.....	Periosteal sarcoma	Osteogenic sarcoma
9	1919	22	♂	Femur, lower end	None.....	Periosteal sarcoma	Periosteal sarcoma
10	1917	14	♀	Femur, shaft.....	Recent fracture.....	Periosteal sarcoma	Periosteal sarcoma
11	1916	19	♂	Femur, lower end	Blow from block of ice; swelling 4 days later	Periosteal sarcoma	Periosteal sarcoma
12	1915	15	♂	Femur, lower end	Bruise, 4 weeks.....	Periosteal sarcoma	Periosteal sarcoma
13	1917	28	♀	Femur, lower end	No.....	Periosteal sarcoma	Periosteal sarcoma
14	January, 1920	22	♂	Femur, midshaft	Recent fracture.....	Sarcoma.....	Sarcoma.....
15	1924	5	♀	Femur, lower end	None.....	Osteogenic sarcoma	Sarcoma.....
16	1919	9½	♀	Femur, upper end	Kick, 2 weeks.....	Periosteal sarcoma, endothelioma	Periosteal sarcoma
17	June, 1919	6	♂	Femur, upper end	Yes.....	Periosteal; metastasis in parietal region	Periosteal sarcoma
18	January, 1917	36	♂	Femur, upper and middle portion	Recent fracture.....	Periosteal sarcoma	Periosteal sarcoma
19	July, 1921	44	♀	Femur, upper end	Fall, few weeks.....	Myeloma.....	Sarcoma; pathologic fracture
20	1918	35	♂	Femur, lower end	Fall, few weeks.....	Sarcoma.....	Periosteal sarcoma
21	1906	12	♀	Femur, lower third	None.....	Sarcoma; treated for rheumatism and tuberculosis 1 year	Inconclusive at that date, 1906
22	1912	27	♂	Femur, upper half	Local injury 1½ years before; pain soon after; tumor 1 year later	Periosteal sarcoma; whole upper half	Periosteal sarcoma

Microscopic Diagnosis	Duration	Treatment	Immediate Result	Final Result
Fibrosarcoma	2 weeks only; circumference 1¼ inches (3.1 cm.) larger than normal size	Toxins 10 days; no effect; hip joint amputation (Coley); no toxins after	Recovery	Lung, metastases 3 months later; died
Inconclusive; infiltration of vessels with large round cells suggesting sarcoma but which might well be tuberculosis (Ewing)	4 months pain; swelling soon after	Exploratory operation; tumor gross appearance typical sarcoma; toxins only treatment given (3 to 4 months)	Recovery	Well 10 years later
Alveolar sarcoma; chiefly round cells; very malignant	3 months.....	Amputation at hip (Coley) April 5, 1897; no toxins after amputation	Recovery	Lung metastases 4 months later; died
Round cell periosteal sarcoma	.....	Toxins (Coley) 2 months; given by Dr. Williamson	Tumor disappeared; limb saved	Well 15 years later
Round cell sarcoma	Few months.....	Local removal, June, 1899 (Coley); recurred in 4 months; hip joint amputation; toxins (Coley) after both operations	Tumor arose from periosteum; bone itself not involved at first operation; remained well 2½ years, then developed metastases	Died 3½ years from onset
Spindle cell osteogenic sclerosing sarcoma	2 months.....	Amputation; toxins 2 to 3 weeks	Recovery	Not traced
Mixed round and spindle cell sarcoma (Ewing)	Few months.....	Amputation after 2 months; toxins and radium given for 6 months after operation	Recovery; no recurrence..	Well 6 years later
Spindle cell sarcoma	3 months.....	Exploratory operation; toxins 2 weeks; amputation; 30 injections of toxins; recurrence, hip joint amputation	Metastases in lung 11 months later	Died
Mixed, spindle, round and giant cells	6 weeks.....	Amputation followed by 17 injections of toxins	Recovery	Not traced
Osteosarcoma	2 months.....	Amputation	Lung metastases 6 months later	Died
Cavernous and myeloid giant cell sarcoma; sclerosing central osteogenic sarcoma of Virchow (Ewing)	.....	Nine roentgen-ray treatments; 12 doses of toxins (Coley); amputation	Recovery; later lung metastases	Died, June 30, 1916
Chondrosarcoma .	1 month.....	Eleven doses of toxins; no effect; amputation, Oct. 8, 1916, followed by toxins (17 doses)	.....	Not traced
Osteosarcoma	1 year.....	Amputation after failure of radium and toxins; toxins 4 months after operation	Recovery; no recurrence..	Well 9 years later
Osteogenic sarcoma	1½ years.....	Toxins and radium.....	.....	Well 7 years later
Malignant, telangiectatic, osteogenic sarcoma	4 months.....	Amputation; toxins		
.....	6 months.....	Toxins and radium.....	Metastases of lung, ilium and sarcoma	Died in less than 1 year
Endothelioma or endothelial myeloma (Ewing)	14 months.....	Toxins and radium over period of 24 years	Disappearance of metastases in parietal and occipital regions; diminution in exophthalmos; no recurrence of tumor in femur; general health excellent	Wel 17 years later
.....	10 months.....	Toxins and radium from October, 1917, to July, 1918	Entire disappearance of tumor; pathologic fracture reunited; limb saved	Well 8 years later
Perithelial sarcoma or plasma cytoma (Mandlebaum); endothelioma; malignant (Ewing)	1½ years; paralysis	Toxins; 1 radium pack, toxins continued by home physician	Recovery; gained in weight; refused further treatment	Metastases 2 years later; died
.....	6 months.....	Toxins for 5 months and radium (about 60,000 millicurie hours)	Refused further treatment	Died 1 year later
Spindle cell, osteogenic sarcoma	1 year pain; tumor 6 months	Rheumatic treatment; plaster cast (elsewhere); March, 1906, exploratory operation; April 7, 1906, amputation; toxins (Coley) begun April, 1906, and kept up for 4 months	Recovery	In good health July, 1926, 20 years later; 3 weeks later (fuller history in text)
Myxochondrosarcoma (Ewing)	Pain 1½ years; tumor only 3 months; very rapidly growing	Regarded inoperable by several surgeons; hip joint amputation March 30, 1912 (Coley); saline infusion after operation; toxins (Coley) given 4 months after operation	Recovery	Well 3 years later

TABLE 7.—*Group I: Patients Treated by Toxins or*

Case	Date	Age	Sex*	Locality	Trauma	Clinical Diagnosis	Roentgen-Ray Diagnosis
23	May, 1909	26	♀	Femur, lower end	Severe blow in 1906; tumor 2 years later	Periosteal sarcoma	Periosteal sarcoma
24	1906	16	♀	Femur, lower end	None.....	Sarcoma.....	Probably sarcoma...
25	November, 1906	10	♂	Femur, shaft.....	None.....	Periostcitis or osteomyelitis; fusiform enlargement of nearly entire shaft (sarcoma, Coley)	Osteomyelitis.....
26	May, 1916	23	♂	Femur, lower third	None.....	Periosteal sarcoma	Periosteal sarcoma
27	February, 1902	19	♂	Femur, shaft, lower two thirds	None.....	Periosteal sarcoma	Periosteal sarcoma
28	March, 1907	9	♀	Femur, lower end	Fall from bicycle; 2 to 3 weeks after	Periosteal sarcoma	Periosteal sarcoma
29	August, 1906	13	♀	Femur, lower end	Fall; swelling 2 weeks later	Periosteal sarcoma	Periosteal sarcoma
30	October, 1908 Sear's case	40	♀	Femur, lower end	Fall on hard floor; pain and swelling soon after	Periosteal sarcoma	Periosteal sarcoma
31	1898 and 1901 Robinson's case	Adult	♂	Femur, lower end	?.....	Sarcoma.....	?.....
32	December, 1907	35	♂	Femur, shaft, middle and upper third	?.....	Periosteal sarcoma	Sarcoma.....
33	September, 1906	35	♂	Femur, lower end	None.....	Periosteal sarcoma	Periosteal sarcoma
34	July, 1897	11	♀	Femur, lower end	Fell down stairs, injuring knee; tumor 3 months later	Periosteal sarcoma	None.....
35	October, 1898	6	♂	Femur, lower end	None.....	Periosteal sarcoma	None.....
36	December, 1909	22	♂	Femur, shaft.....	None.....	Periosteal sarcoma	Periosteal sarcoma
37	1915	25	♀	Femur, lower end	Sprain 2 weeks before	Periosteal sarcoma	Periosteal sarcoma
38	1915	18	♀	Femur, lower end	Recent fracture.....	Periosteal sarcoma	Sarcoma.....
39	1913	20	♂	Femur, lower end	None.....	Periosteal sarcoma	Periosteal sarcoma

Microscopic Diagnosis	Duration	Treatment	Immediate Result	Final Result
Biopsy report: myositis ossificans (Ewing) or chronic formative osteitis, giant cell sarcoma	Injury, 1906; tumor, 1908; no pain	In view of gross and microscopic examination of specimen removed at biopsy showing no evidence of malignancy, no treatment was given in 1909		
Giant cell sarcoma	Pain, 3 months; tumor, 2 months	Toxins 1 month; decrease in size 1 inch (2.5 cm.); later increase; amputation (Coley) (Hospital for Ruptured and Crippled) May 18, 1906	Toxins after amputation, 32 doses; rapid gain in weight	Remained well for 3 years, then developed metastases in pelvic bones and lung; died in 3½ years
Round cell sarcoma (biopsy)	Pain, 1 year; tumor, 2 months; loss of weight; temperature, 102 F.	Toxins (Coley) begun January, 1907; circumference of tumor decreased from 11¾ to 9$^{15}/_{16}$ inches (29.7 to 25 cm.); 57 injections of toxins in 1907	Did very well for a year, then developed metastases of brain with exophthalmos, double, no recurrence of femur tumor	Died 1½ years after treatment
Lower end of femur hard, ivory-like formation; narrow cavities obliterated; cells few and elongated; spindle shaped tissue; does not appear very active (Ewing)	Pain and disability 10 years before; tumor soon appeared; local removal 8 years before; second operation, January, 1916 (Deaver); pathologic diagnosis: ostema; recurred promptly	Toxins (Coley) 8 doses; no improvement; amputation below trochanter (Coley), July 8, 1916; toxins kept up 2 to 3 months after operation	Recovery	Remained well for 3 years, then developed lung metastases; died
Round cell sarcoma (Dr. E. K. Dunham, Carnegie Laboratory)	3½ months.....	Hip joint amputation advised and refused; 4 roentgen-ray treatments, February to December, 1902; metastases in pelvic region in 1903; 3 to 4 inches (7.6 to 10.1 cm.) removed; pronounced round cell sarcoma; also extensive metastatic tumor in ilium, January, 1903, toxins (Coley) given at this time; 86 injections in 6 months, 170 roentgen rays to ilium	Large tumor in ilium broke down; incision and drainage; complete disappearance; tumor of thigh showed epithelioma and large round cell sarcoma; tumor in medullary cavity of bone epithelioma	Well May, 1912, 10 years later; then developed tumor in old roentgen-ray burn; excision; pronounced epithelioma; extensive tumor developed in soft part of burn; amputation at thigh, January, 1913; died; metastasis of lung 2 to 3 weeks later
Mixed spindle and round cell sarcoma	Tumor observed only 1 week (father a physician); one side 2 inches (5 cm.) larger than other	Toxins 2 weeks, then amputation below trochanter (Coley); toxins resumed	Recovery	Developed lung metastases 13 months later; died
Osteosarcoma	6 weeks.....	Amputation below trochanter August 31, 1906; toxins for 4 months after	Recovery	Well 4½ years, then developed metastases in pelvis and lungs; died Dec. 3, 1910
Osteogenic sarcoma (Ewing)	6 months pain; tumor soon after	Amputation below trochanter (Dr. A. I. Bevan); toxins (Coley) for 9 months after amputation	Recovery	In good health December, 1924, 18 years
Osteosarcoma	Few months.....	Hip joint amputation (Dr. J. A. Wyeth) 1908; toxins short time under Dr. Coley's direction; well 3½ years	Recurrence in stump and iliac fossa; toxins resumed; tumor broke down; drained	Well several years later
Small round cell sarcoma	Few months.....	Partial local incision before coming to Memorial Hospital; regarded as inoperable; toxins for 3 months	Considerable improvement; amputation shortly after by D. J. Bolling Lee	Well 2 years later
Round cell sarcoma (biopsy)	6 months pain.....	Amputation below trochanter (Dr. John Erdman) September, 1906; toxins (Coley) 3 to 4 months	Recovery	Well, July, 1926, 16 years later
Round cell sarcoma	2 months.....	Hip joint amputation (Coley), July, 1897; no toxins after operation	Recovery	Not traced beyond 6 months
Small round cell sarcoma	6 months.....	Amputation hip joint (Coley); no toxins	Recovery	Lung metastases 6 months later; died
Round cell sarcoma (Presbyterian Hospital laboratory); endothelioma (Ewing)	Few weeks; local removal (Dr. Hortenwell) August, 1909; recurred; treated at Memorial Hospital with toxins, December, 1909; improved, then increased; amputation (Dr. J. A. Blake)	Referred back to Coley for toxins after amputation; toxins given in two periods for 4 months	Recovery	Well, December, 1924, 15 years later
Periosteal spindle cell sarcoma	3 months.....	Amputation below trochanter; refused toxin treatment as prophylactic	Local recurrence 3 years later	Died 6 months later
Osteogenic, spindle and round cell sarcoma	3 months.....	Hip joint amputation (Coley); no prophylactic treatment	Metastases in lungs 4 months later	Died
Round cell sarcoma	6 months.....	Amputation (Dowd)	Metastases in lung 14 years later	Died

TABLE 7.—*Group I: Patients Treated by Toxins or*

Case	Date	Age	Sex	Locality	Trauma	Clinical Diagnosis	Roentgen-Ray Diagnosis
40	1911	37	♂	Femur, lower end	Severe blow; soon...	Periosteal sarcoma	Periosteal sarcoma
41	1916	48	♂	Femur, shaft.....	Fracture at age of 4 years; fracture at 11 years; periostitis at 21 years	Periosteal sarcoma	Sarcoma.....
42	June, 1924	6½	♀	Femur, lower end	Fall 2 months before	Sarcoma.....	Sarcoma.....
43	August, 1919	13	♀	Femur, shaft.....	Fall, followed by swelling 1 month later	Sarcoma.....	Periosteal sarcoma
44	December, 1919	8	♂	Femur, lower end	.....	Periosteal sarcoma	Periosteal sarcoma
45	January, 1920 Packard's case	5	♂	Femur, upper end	Fall; tumor soon after	Sarcoma (negative Wassermann and Pirquet reactions)	Osteosarcoma.....
46	March, 1925	20	♂	Femur, shaft, upper third	Severe squeeze in subway door; swelling soon after	Osteoma.....	Sarcoma ?.....
47	April, 1925	21	♀	Femur, midshaft	Automobile accident; local injury few weeks	Periosteal osteosarcoma	Periosteal sarcoma with marked production of new bone
48	January, 1925	30	♂	Femur, midshaft	None.....	Osteomyelitis.....	Osteomyelitis.....
49	1923	35	♂	Femur, midshaft	?.....	Periosteal sarcoma	Periosteal sarcoma
50	1898	25	♂	Femur.....	Severe strain.....	Periosteal sarcoma	.....
51	1909 Willmoth's case	28	♂	Femur, middle and upper third	Injured thigh.....	Periosteal sarcoma	Sarcoma.....
52	1909	26	♀	Tibia.....	Fall 3 years before	Sarcoma.....	.....
53	1915	16	♀	Tibia.....	Fall through ice.....	Periosteal sarcoma	.....
54	February, 1899	27	♂	Tibia, midshaft...	None.....	Periosteal sarcoma	None.....
55	April, 1906	20	♂	Tibia, lower end	Sprain 4 years before	Sarcoma.....	Inconclusive, probably sarcoma
56	June, 1907	30	♀	Tibia, upper end	None.....	Osteitis.....	Doubtful.....

Radium and Toxins or Amputation and Toxins—Continued

Microscopic Diagnosis	Duration	Treatment	Immediate Result	Final Result
Myxosarcoma	1 year.....	Toxins 4 weeks; amputation (Bristow)	Well few months later....	Not traced
Large spindle and giant cell sarcoma (Ewing); spindle cell osteogenic sarcoma (Wood)	Enlargement noticed 2 months before operation	Local removal; curettage; roentgen-ray treatments; temporary improvement; toxins and radium (2,000 millicurie hours at 2 cm. distance); no improvement; amputation followed by toxins for a number of months	Recovery	Well 10 years later
.....	Pain 2 months.....	High voltage roentgen rays (4 treatments); toxins	No improvement	Metastases 5 months later; in this case the disease was very far advanced when treatment was begun
No biopsy	Swelling 5 months	Radium (31,416 millicurie hours); toxins, 18 injections; amputation advised but refused	Not improved	Not traced
No biopsy	.....	Toxins; radium (101,693 millicurie hours); roentgen rays, 12 treatments in 1 month	Rapid generalization of disease; metastases in head and lungs	Died in July, 1920
No biopsy; too far advanced for exploratory operation	3 months severe pain; extensive destruction upper third femur; patient emaciated and bedridden, quite inoperable; bed sores; dilation superficial	Toxins (Coley) begun by Dr. Packard, Denver, Jan. 6, 1920; kept up until June 30, 1920; 93 doses	Immediate and rapid improvement March 1; no pain; patient in wheel chair; bed sores healed; dilated veins disappeared; June 15, walked with crutches; October 1, discharged in normal health	October 1, plaster spica; January, 1921, able to work; in good health 5 years later
1. Mixed cell sarcoma (Jeffries); 2. Osteogenic sarcoma, polygonal cell, malignant (Ewing)	4 months.....	Osteotomy at Jewish Hospital; toxin treatment at Hospital for Ruptured and Crippled	Entire disappearance of tumor; patient in excellent condition 3 months later	Well, July, 1926
No biopsy	3 to 4 weeks.....	Roentgen rays; 2 weeks later, toxins and radium	Decreased ¾ inch (1.8 cm.) in size; no further improvement; amputation advised and refused	Not traced
Osteitis, biopsy 1; osteitis, biopsy 2; sarcoma, biopsy 3; sarcoma, endothelial myeloma type (Ewing)	5 months.....	(1) Exploratory operation and curettage August, 1924; (2) exploratory operation and removal of bone January, 1925; (3) exploratory operation July, 1925; (4) amputation July 30, 1925 (B. L. Coley); had few doses toxins before amputation, while getting consent to amputate; toxins after amputation	Recovery	Well at present time, July, 1926
Biopsy: endothelioma (Ewing)	Few weeks.....	Toxins 3 weeks at Hospital for Ruptured and Crippled; not much improvement; amputation advised, refused; left hospital	Was treated elsewhere; character of treatment not known	Died about 3 months later
Periosteal sarcoma	3 months.....	Amputation of hip joint (Drs. W. T. Bull and W. B. Coley)	Recurred in 4 months in pelvic bones and stump; toxins for brief period without marked effect	Died in 8 months; metastases of lung
Round cell sarcoma	8 months.....	Curettage; toxins at periods (2 months and 5 weeks)	Recovery	Well 16 years later
Round and spindle cell sarcoma, giant cell	2 years.....	Exploratory operation; amputation by Dr. Wm. T. Buel	Recovery	Died 6 years later, lung metastases
Mixed cell sarcoma	3 months.....	Two operations by Dr. W. Lindes; roentgen rays and toxins before second operation	Recovery	Well 11 years later
(Prof. John Cavern, Toronto University) spindle cell sarcoma	First noticed tumor of tibia, July, 1897, operation (Dr. Stewart of Toronto) November, 1898; local removal, slow healing, recurrence in 6 weeks	Amputation advised by several surgeons; admitted to Memorial Hospital, February, 1899; treated with toxins (Coley); later while in hospital developed typical attack of erysipelas over affected leg	Ulcerated area healed; evidence of tumor disappeared; regained health	In good condition, limb saved, well, July, 1926, 27 years later
Biopsy: round cell sarcoma	July, 1905, pain; December, 1905, unable to work because of limp and pain	Exploratory operation; bone marrow absent for 6 inches (15.2 cm.) above malleolus, replaced by clear fluid; extensive swelling of lower half of tibia; toxins (Coley) April to July, 1906	Tumor decreased 1 inch (2.5 cm.) in size	Well when last seen more than 1 year later; unable to trace further
Biopsy: chondrosarcoma	Pain 6 months; tumor 1 year	January, 1907, admitted to Hospital for Ruptured and Crippled; first operation, Newburg Hospital, August, 1906, called cyst; second operation, Hospital for Ruptured and Crippled, tumor size of egg, reddish pulp like material seen in giant cell sarcoma; toxins, January to September, 1906; roentgen rays three times a week for 2 months	Rapid recurrence apparently controlled by treatment; later increase in size; amputation advised in June, but patient would not give his consent until October; performed by Dr. R. Whitman; toxins after amputation	Metastases 1 year later; died

TABLE 7.—*Group I: Patients Treated by Toxins or*

Case	Date	Age	Sex	Localtiy	Trauma	Clinical Diagnosis	Roentgen-Ray Diagnosis
57	October, 1913	30	♂	Tibia, upper end	Wrenched knee playing golf 1 year before; no tumor until 10 months later	Sarcoma, malignant	Central sarcoma.....
58	June, 1910	27	♀	Tibia, shaft.....	Fall 2 months before	Periosteal sarcoma	Periosteal sarcoma
59	March, 1913	12	♀	Tibia, shaft.....	Local injury August, 1911; swelling 3 months later	Sarcoma ? syphilis ?	Inconclusive.....
60	December, 1921	17	♂	Tibia, upper end	No definite trauma	Central sarcoma with periosteal involvement	Central sarcoma.....
61	January, 1915	35	♂	Tibia, upper end	None.....	Periosteal sarcoma	Periosteal sarcoma
62	August, 1915	21	♀	Tibia, upper end	None.....	Central sarcoma.....	Central sarcoma.....
63	October, 1916	8	♀	Tibia, shaft, middle two thirds	None.....	Osteitis or periostitis, periosteal sarcoma ?	Irregularity and thickening of periosteum
64	April, 1917	30	♂	Tibia, middle and lower third	None.....	Periosteal sarcoma	Periosteal sarcoma
65	April, 1919	16	♂	Tibia, upper end	None.....	Periosteal sarcoma	Periosteal sarcoma
66	December, 1922	19	♂	Tibia, upper end	Fell from ladder, injuring upper part of tibia. tumor in 1 week	Periosteal sarcoma	Periosteal sarcoma
67	June, 1922	22	♀	Tibia, lower end	None.....	Central sarcoma.....	Central sarcoma.....
68	July, 1919	55	♂	Tibia, middle and upper third	Fracture 4 years before	Sarcoma, resembles endothelioma (Coley) type	Extensive destruction of bone involving both central and periosteal portions (Dr. D. Quick)
69	October, 1921	15	♂	Tibia, upper end	Local injury; struck by baseball 1 week	Periosteal sarcoma	Periosteal sarcoma

Radium and Toxins or Amputation and Toxins—Continued

Microscopic Diagnosis	Duration	Treatment	Immediate Result	Final Result
Spindle cell central osteogenic sarcoma; few atypical giant cells; tumor more malignant than ordinary central sarcoma of epulis type (Ewing)	2 months.....	Exploratory operation. Oct. 24, 1913; toxins begun October 27; patient extremely nervous and in great pain; only few doses toxins given before pain was relieved; slight decrease in size	Nov. 17, 1913, pain returned; slight increase in size; amputation Nov. 22, 1913 (Coley); patient refused further toxin treatment	June, 1915, extensive metastases in ribs; died few months later
Round cell sarcoma	14 months.....	Large tumor involving whole central part of tibia; toxins 3 to 4 weeks, then amputation at midthigh (Coley); toxins 1 month after operation	October, 1910, recurrence in stump	Metastases in lung following year; died
Small round cell sarcoma	1 year.....	First operation, December, 1912 (Dr. G. D. Stewart); condition believed to be syphilitic; no microscopic examination; biopsy, Jan. 3, 1913; Feb. 3, 1913, amputation (Dr. Stewart); toxins after amputation (Coley)	Recovery; toxins continued by family physician for few weeks	Died; metastases 1 year later
Very malignant sarcoma; mixed large polyhedral giant cells with much hyaline substance (Ewing)	2 months.....	First operation 1 week after swelling noticed, by Dr. McLane, Scranton, Pa.; cavity upper end of tibia containing soft red mottled tissue, had broken through bony structure; local recurrence 1 month; admitted Hospital for Ruptured and Crippled, Dec. 15, 1921	Toxins and radium 3 weeks; no improvement; amputation (Dr. B. L. Coley) Jan. 15, 1922; toxins a short time after operation	Metastases in lungs; died, October, 1921
Chondrosarcoma; many mononuclear giant cells (Ewing)	2 months.....	Six doses toxins (Coley) given before operation; no improvement; amputation (Dr. Brownlee, Danbury, Conn.) Feb. 8, 1915; toxins given few weeks after amputation	Recovery	Lung metastases 6 months later; died
Round cell osteosarcoma; considerable malignancy (Ewing); final report: spindle cell sarcoma	5 months.....	Biopsy, April 15, negative; biopsy, June 15, negative; biopsy, Aug. 8, 1915, central tumor not involving joint; toxins 3 months, no improvement; amputation (Coley) March, 1916	Recovery; metastases in pelvic bones 6 months later; grew to enormous size	Died 1 year after amputation
Small round cell sarcoma (Ewing)	4 months.....	Toxins begun October 30; radium pack (3,000 millicurie hours at 6 cm. distance) November 14; two other radium treatments November and December	Very rapid disappearance of tumor; February, 1917, leg practically normal; March, 1917, recurrence	Died, lung metastases, July, 1917
1, small spindle cell osteogenic periosteal sarcoma (Ewing); tumor of quite malignant structure; 2, metastatic tumor examined September, 1917; actively growing sarcoma (Ewing)	3 weeks.....	Toxins begun April 7, 1917; radium May 1-8, 1921; June 19, a total of 46,720 millicurie hours at 6 cm. distance; decrease in size 1 inch (2.5 cm.) in first month; toxins kept up until August, then discontinued until September, 1923	Tumor entirely disappeared by June, 1917; September 23, extensive metastases in femoral, inguinal and iliac glands; toxins resumed and radium applied to groin and iliac fossa in October, November and December, total of 47,970 millicurie hours at 10 cm. distance; toxins kept up 24 hours	Patient in good health December, 1924, 9 years later; limb saved
Large polyhedral cell sarcoma resembled perithelioma; no bone production (Ewing)	Few months.....	Toxins, April to September, 1919; marked improvement at first, then slight increase in size; radium treatment Sept. 19, 1919; toxins and radium kept up until June, 1920; tumor not controlled; amputation (Coley) Aug. 18, 1920; toxins after amputation	Recovery	March 1, developed metastases in skull and mediastinum and probably lungs; died 1 month later
Periosteal chondrosarcoma (Ewing)	3 weeks.....	Amputation, Dec. 22, 1922 (Dr. Kleinberg, Hospital for Ruptured and Crippled); toxins (Coley) after operation, kept up for 2 to 3 months; roentgen-ray examination Nov. 13, 1923, for first time, showed metastases in left lung; toxins resumed; September, roentgen-ray treatment to chest	Metastatic nodules on lung controlled by toxins and radium until April, 1924; condition then grew worse	Died in beginning of 1925
Osteosarcoma; not the so-called giant cell sarcoma giant cell, Ewing (Mandlebaum)	Slight increase in size 6 years before; recent increase in size	Operation, March, 1922 (Dr. H. Lilienthal), curetted tumor and implanted fat; toxins given soon after operation and continued later by Drs. Coley and S. Stedman of San Francisco	Recovery; no recurrence	Well, August, 1926, 4 years later, limb normal
No biopsy	Pathologic fractures 2 weeks before; pain few days before	Toxins and radium treatment (Memorial Hospital, Coley)	Complete recovery	Patient well, July, 1926, 7 years later
Sarcoma, osteogenic	.....	Toxins and radium 2 months; tumor not controlled; amputation (Dr. B. L. Coley) Oct. 21, 1921; toxins after amputation	Recovery	In good health, July, 1926, 4 years 10 months later

TABLE 7.—*Group I: Patients Treated by Toxins or*

Case	Date	Age	Sex	Locality	Trauma	Clinical Diagnosis	Roentgen-Ray Diagnosis
70	October, 1924	18	♂	Fibula, upper end	.....	Periosteal sarcoma	Periosteal sarcoma
71	March, 1920	8	♂	Fibula, lower end	January, 1920, blow to outer side leg; pain few days later; swelling soon after	Osteomyelitis (Hospital for Ruptured and Crippled); sarcoma, very extensive (Coley)	Periosteal sarcoma; metastases
72	April, 1918	21	♂	Fibula, upper end	?.....	Periosteal sarcoma	Periosteal sarcoma
73	August, 1920	12	♂	Fibula, upper end	None.....	Osteomyelitis following operation for suppurating appendicitis	Doubtful at first; periosteal sarcoma; Aug. 8, 1920, roentgen rays showed no recurrence
74	1921	14	♂	Fibula, upper end	None.....	Periosteal sarcoma	Periosteal sarcoma; suggested possible endothelioma
75	1921	16	♂	Tibia, upper end	.....	Periosteal sarcoma	Periosteal sarcoma
76	1898	30	♀	Fibula.....	?.....	Periosteal sarcoma	None.....
77	June, 1917	7	♀	Tibia, midshaft	No.....	Periosteal sarcoma	Periosteal sarcoma
78	May, 1925	6	♀	Tibia, upper end	Six months before injured in automobile accident; tumor 4 months later	Periosteal sarcoma	Periosteal sarcoma
79	March, 1925	13	♀	Tibia, upper end	Three months.....	Periosteal sarcoma; first diagnosis: syphilitic periostitis	Periosteal sarcoma; first roentgenogram: syphilis
80	1898	25	♀	Humerus, upper end	Few months.....	Periosteal sarcoma	None.....
81	July, 1907	15	♀	Humerus, upper end	Old injury 10 years before	Periosteal sarcoma	Periosteal sarcoma; really inoperable as it was impossible to get around tumor by operation
82	March, 1910	10	♂	Humerus, upper end	Fell on ice; fracture 5 weeks before	Central sarcoma, malignant	Central sarcoma.....
83	November, 1906	13	♀	Humerus, upper end	None.....	Periosteal sarcoma	Periosteal sarcoma
84	February, 1904	28	♂	Humerus, upper end	None.....	Periosteal sarcoma	Periosteal sarcoma

Radium and Toxins or Amputation and Toxins—Continued

Microscopic Diagnosis	Duration	Treatment	Immediate Result	Final Result
Osteogenic sarcoma (Ewing)	6 weeks pain.....	Toxins and radium (Memorial Hospital, Coley) Oct. 28, 1924 for 3 weeks, no improvement; amputation advised, refused; resection (Dr. Fred Albee) December, 1924; referred back to Dr. Coley for toxins after operation	Operation showed extensive osteogenic sarcoma with separate nodules in muscles of calf; recovery in 1925; amputation (Coley)	Well at present, July, 1926
Round cell sarcoma (Jeffries and Ewing); revised diagnosis: endothelioma (Ewing); tumor in groin; round cell sarcoma	6 weeks.....	Biopsy March, 1920; clinical and microscopic diagnosis: osteomyelitis, round cell sarcoma, very rapid growth, enlarged glands in groin; amputation (Dr. R. Whitman) June 1, 1926; toxins (Coley) June to August	Growth in groin excised; microscopic diagnosis: sarcoma; October 27, extensive metastatic tumor in iliac fossa, 1 dose radium (10,108 millicurie hours); lung metastases October, 1920	No further treatment; complete recovery; well July, 1926, 6 years 4 months later
Biopsy: malignant osteogenic sarcoma, giant cell (Ewing)	.....	Toxins and radium 2 months; no improvement; amputation (Coley) followed by toxins	Recovery	Metastases in lung 8 months later; died
Chondrosarcoma, cellular, malignant (Ewing)	5 months.....	First operation, scraping bone, January, 1920; recurrence 2 months; resection 6 inches (15.2 cm.) shaft, August, 1920; local recurrence; third operation, whole fibula removed except little piece near knee joint; toxins and radium August, 1920; radium pack (44,029 millicurie hours) and bare tubes	Roentgen-ray examination, December, 1920, showed calcareous areas site of fibula; possible recurrence April, 1921; undoubted recurrence; amputation (Coley) April 6, 1920; toxins after operation	Metastases in lung; died, September, 1921
Osteogenic sarcoma (Ewing)	Small size swelling in few weeks	Toxins and radium at Memorial Hospital, 3 months (Coley)	Marked improvement; while still improving locally, developed metastases in lungs 3 to 4 months later	Died 6 months later; metastases in lung and local recurrence
Osteogenic sarcoma (Ewing)	Few weeks.....	Toxins and radium 3 months at Hospital for Ruptured and Crippled; marked improvement soon noted; tumor disappeared in 4 months	Developed local radium burn	Two years later developed activity in tuberculous process in lung; no recurrence of sarcoma 5 years later; limb saved; lung condition progressed; died, November, 1925
Spindle cell sarcoma	6 months.....	Toxins few weeks; later amputation	.....	Died; metastases in lung in less than 1 year
1, periosteal sarcoma (pathologist Toronto General Hospital); 2, diffuse endothelioma (Ewing)	6 months.....	Roentgen-ray radiation before coming to Memorial Hospital, then toxins, amputation and toxins	Prompt recovery	Well 8 years later
Osteochondrosarcoma	4 months.....	Biopsy, April 5, 1925, by Dr. Cunningham Wilson; four roentgen-ray treatments (deep therapy) to groin	Rapid increase in size in spite of roentgen rays; amputation, May 9, by Dr. W. B. Coley, followed by prophylactic toxins	Died, metastases of lung, September, 1925
Osteogenic sarcoma (Ewing)	4 weeks.....	Treated 4 weeks with toxins and radium (Coley); no effect; amputation advised and refused; roentgen ray and radium given elsewhere 3 months	Readmitted to Hospital for Ruptured and Crippled, June 1, 1925; amputation by Dr. B. L. Coley, followed by toxins	Well, August, 1926
Osteosarcoma, large, round cell (F. B. Mallory)	Few months.....	Interscapular thoracic amputation advised but refused; exploratory operation (Dr. Blake) glenoid portion of scapula involved; prolonged toxin treatment under Dr. Coley's direction	Complete recovery; restoration of function; limb saved	In good health for 24 years, then developed metastases in spine; died
Round cell sarcoma	Pain 6 months; swelling 5½ months	Very extensive tumor involving two-thirds of humerus; toxins for 2 weeks; amputation, interscapular thoracic (Coley), July, 1907; toxins for 2 or 3 months	Axillary and subclavian vein filled with tumor; thrombus showing amputation did not get beyond disease and it was really an inoperable case	April, 1907, developed lung metastases; died, May 10, 1908
Benign giant cell sarcoma epulis type (Ewing)	5 weeks before; believed to be redundant Colles' fascia following fracture	Immediate amputation without biopsy (Coley); clinical history and physical signs regarded as proof of highly malignant tumor	Toxins given twice a week and later once a week until September, 1920	June, 1911, developed weakness and signs of lung metastases; died, Aug. 30, 1921
Biopsy: round cell sarcoma	3 months.....	Toxins, 3 weeks, no improvement; amputation advised by Coley but refused	Patient left hospital.....	Developed metastases few months later; died
Round cell sarcoma	4 months swelling	Treated in early stage by one physician as a dislocation and some violence used to reduce it; then mechanical massage; when admitted to Memorial Hospital, Feb. 3, 1904, tumor was very large, almost inoperable; patient emaciated	Amputation (Coley) Feb. 5, 1907; recovery; toxins and roentgen rays given	Soon developed metastases in spine and probably in lungs; died June 26, 1904

TABLE 7.—*Group I: Patients Treated by Toxins or*

Case	Date	Age	Sex*	Locality	Trauma	Clinical Diagnosis	Roentgen-Ray Diagnosis
85	June, 1910	35	♂	Humerus, midshaft	January, 1910, spinal fracture from fall; roentgen ray showed no pathologic condition at time; 3 weeks later, sarcoma	Periosteal sarcoma	Periosteal sarcoma
86	February, 1908	17	♀	Humerus, shaft	Puncture of forearm 6 weeks before with needle; 1 week later swelling noted higher up in arm; probably no connection	Subperiosteal abscess	Doubtful.....
87	May, 1915	16	♀	Humerus, midshaft	None.....	Periosteal sarcoma	Periosteal sarcoma
88	May, 1912	15	♂	Humerus, upper end	None.....	Periosteal sarcoma	Productive and destructive process, probably sarcoma (Cole)
89	May, 1914	50	♂	Humerus, upper end	None.....	Inflammatory rheumatism at first, periosteal sarcoma, May, 1914, inoperable	Periosteal sarcoma
90	November, 1916	35	♂	Humerus, upper end	Local injury 1½ years before	Bursitis after first; later, periosteal sarcoma	Tumor of soft parts with secondary involvement of periosteum (Holding)
91	October, 1916	56	♂	Humerus, upper end	Severe blow with iron bar, upper arm, 14 years before	Periosteal sarcoma	Periosteal sarcoma
92	February, 1918	24	♂	Humerus, upper end	Severe strain on shoulder; tumor in few weeks	Sarcoma.....	Sarcoma.....
93	October, 1917	17	♀	Humerus, upper end	August, 1917, fell, striking on shoulder; pain 1 month later	Periosteal sarcoma	Typical periosteal sarcoma
94	November, 1918	40	♂	Humerus, upper end	Struck point of shoulder against corner, June, 1918; 1 month later pain and stiffness	Periosteal sarcoma	Cyst with probable malignant change
95	February, 1917	40 colored	♂	Humerus, upper end	None.....	Periosteal sarcoma	Periosteal sarcoma
96	June, 1924	19	♀	Humerus, upper end	None.....	Diagnosis, May 22, 1924, bursitis; June 24, periosteal sarcoma	May 24, 1924, roentgen-ray examination negative; June 24, periosteal sarcoma

Radium and Toxins or Amputation and Toxins—Continued

Microscopic Diagnosis	Duration	Treatment	Immediate Result	Final Result
Spindle cell osteogenic sarcoma (Ewing)	Severe pain 3 weeks after fracture; second roentgenogram showed well developed tumor at site of fracture	June, 1910, exploratory operation by Dr. J. M. T. Finney, who found a large sarcoma involving the periosteal and central portions; pathologic fracture; believed amputation offered little hope; referred patient to Coley for toxins; toxins begun June 9, 1910	By November, 1910, tumor had disappeared; fracture united; December, 1910, signs of recurrence near head of humerus; amputation at shoulder joint (Coley) January, 1911; large tumor recurred in pectoral region; 6 months later, incomplete removal; prolonged toxin treatment	Patient remained well for 8 years; in 1920 he developed metastases in lungs; died in a few months
Osteosarcoma with spindle cells predominating (Dr. John Funke, Jefferson Hospital, Philadelphia)	5 weeks of pain; swelling soon after	Exploratory operation, Feb. 15, 1908, by Dr. John Gibbons of Philadelphia; mass size of egg removed from lower inner surface of humerus; microscopic diagnosis: osteosarcoma; amputation advised but refused; treated with toxins under Dr. Coley's direction, combined with roentgen rays for several months	Tumor recurred in early March; disappeared under treatment	Well 16 years later; limb saved
Myxochondrosarcoma, biopsy, November, 1914	8 months.....	Roentgen rays 2 months before coming to Memorial Hospital; 2 weeks toxin treatment; Dr. Coley then advised amputation; patient left hospital; later amputation in June, 1915	Recovery	Not traced
Spindle cell sarcoma (biopsy)	2 years pain.....	Toxins for 2 to 3 weeks at Memorial Hospital; continued at home; patient refused amputation; toxins kept up 6 weeks	Improved at first; later tumor increased in size; metastases developed	Died, October, 1912
Osteochondrosarcoma, malignant (Ewing)	5 months pain; later swelling; lost 40 pounds (18.1 Kg.) weight since January	Condition believed inoperable, June 1, 1914, ligature of subclavian artery (Coley); June to August, 28 doses of toxins (Coley); decrease in circumference 1¾ inches (4.3 cm.) by June 28; August 11, interscapular thoracic amputation (Coley); roentgen-ray treatment and toxins after amputation	Recovery; temporary improvement; Dec. 18, 1914, metastases in liver (lungs free)	Died, May, 1915
Sarcoma; tumor peculiar and different from common bone sarcoma; probable diagnosis: myxosarcoma (Ewing)	Pain soon after injury; 1½ years later swelling	Amputation advised by Coley and Downes, but refused by patient; treated with toxins and radium; 40 injections of toxins; 1,800 millicurie hours radium at 3 cm. distance	No improvement	Left hospital; not traced
Small round cell sarcoma	6 months swelling with little pain	Refused early amputation; treated with toxins and radium for 5 weeks (very large tumor); November, 1916, amputation by Dr. Charles Stewart of Newport, R. I.; no toxins after	Recovery	Metastases 3 months later; died
None	1 month pathologic fracture; metastatic tumor in lung	February, 1918, exploratory operation by Dr. Mackid of Calgary, Canada; large amount of gelatinous tumor tissue removed; patient put on toxins (Coley) for 4 months	Wound healed; fracture reunited; tumor disappeared; toxins discontinued from July to November, then resumed for another period	Well at present, 8 years later
.....	1 month.....	Toxins and radium at Memorial Hospital	Disease not controlled....	Lung metastases 5 months later; died
Mixed cell sarcoma (Mayo Clinic laboratory)	4 months.....	Resection upper third humerus (Mayo Clinic, Dr. H. W. Meverding), Oct. 18, 1918; radium treatment 3 weeks then referred to Dr. Coley for toxins; toxins begun Dec. 3, 1918, and continued at home; no marked reaction	Jan. 9, 1919, roentgen ray showed large fusiform mass attached to seventh rib, bulging into chest cavity; radium pack applied (12,000 millicurie hours at 6 cm.)	Metastases developed in femur; died in about 8 months
Osteogenic sarcoma (Ewing)	2½ months pain and stiffness	Amputation advised and refused; Feb. 8, 1917, exploratory operation; toxins and radium for few weeks; disease not controlled; amputation (Coley)	.....	Metastases in lungs 6 months later; died
No biopsy	5 months; loss of abduction first symptom	Baking, electricity and massage 6 weeks on diagnosis of bursitis; referred to Dr. Coley, June 24, 1924; amputation advised but refused as she was several months pregnant; toxins, radium and roentgen rays given at Memorial Hospital	Tumor apparently entirely disappeared in 2 months; recurred in October; further roentgen-ray treatment; very rapid and remarkable decrease in size; circumference over tip of clavicle and axilla diminished 5 inches (12.7 cm.) in 4 weeks; in 6 weeks arm was practically normal; toxins continued at home	Dec. 2, 1924, not increasing in size; firm metastases, summer of 1925

TABLE 7.—*Group I: Patients Treated by Toxins or*

Case	Date	Age	Sex	Locality	Trauma	Clinical Diagnosis	Roentgen-Ray Diagnosis
97	July, 1924	47	♂	Humerus, upper end	May 15, 1924, spinal fracture upper third humerus; December, 1924, swelling and pain	Periosteal sarcoma	Periosteal sarcoma
98	November, 1917	21	♂	Humerus, upper end	None.....	Osteomyelitis (Hospital for Ruptured and Crippled)	Periosteal sarcoma
99	December, 1920	19	♂	Radius, lower end	Repeated trauma; riveter by occupation; constant vibration of wrist	Periosteal sarcoma	Periosteal sarcoma
100	April, 1913	15	♀	Radius, lower third of shaft	Severe wrench of arm 5 years before; swelling 1 year later	Periosteal sarcoma	Periosteal sarcoma
101	July, 1919	8	♂	Ulna, midshaft	Fell on pile of bricks; swelling of forearm noted soon after	Periosteal sarcoma (Coley)	Syphilitic osteitis (at one hospital); "peculiar condition, diffuse rarefying process with partial occlusion of the medullary cavity; periosteum thickening" (Quick)
102	July, 1908	15	♂	Ulna, upper end	Fracture 7 months; later swelling	Sarcoma.....	Sarcoma.....
103	September, 1914	22	♂	Radius, lower end	None.....	Central sarcoma.....	Central sarcoma.....
104	1908	34	♂	Clavicle, middle and inner third	Severe blow from falling plank 6 to 7 years before	Periosteal sarcoma	.....
105	1909	16	♂	Clavicle, middle two thirds	Severe strain; swelling in 2 to 3 weeks	Periosteal sarcoma	Periosteal sarcoma
106	May, 1924	11	♀	Clavicle.....	Fell, striking shoulder on hard floor February, 1924; pain and swelling 2 or 3 weeks later	Periosteal sarcoma	Periosteal sarcoma
107	August, 1917	16	♂	Mastoid.....	?.....	Sarcoma.....	Sarcoma.....
108	March, 1917	16	♀	First rib, left side	None.....	Sarcoma.....	Sarcoma.....
109	1898	18	♀	Metatarsal bone	?.....	Sarcoma.....	None.....

Microscopic Diagnosis	Duration	Treatment	Immediate Result	Final Result
No biopsy	6 months pain.....	Referred by Dr. John B. Deaver with a very large tumor of left shoulder; border line of operability; toxins directly into tumor and radium pack applied	Improvement; slight recurrence in November, 1924; further radium treatment in December, 1924	Well, July, 1926, 2 years later
.....	2 months.....	Exploratory operation (Coley) Nov. 19, 1917; large amount of soft reddish tumor tissue resembling myeloid sarcoma removed; thorough curetting of cavity; phenol (carbolic acid) applied; toxins and radium given in large doses	Tumor not controlled; grew rapidly	Died, Feb. 19, 1918
Fibrosarcoma (Jeffries)	3 months pain.....	Exploratory operation (Coley) Jan. 5, 1920; toxins alone 2 weeks; decrease 1¼ inches (3.1 cm.) in size; toxins and radium continued until April, 1920; disease under apparent control	Patient later under Dr. J. C. Bloodgood's care; further radium treatment; metastases in axilla in August; later lung metastases	Died
Periosteal spindle cell sarcoma (Ewing)	2 to 3 years.....	Treated at Massachusetts General Hospital 2 to 3 years before; roentgen rays; improvement; recurrence in 6 months; amputation advised (Dr. Monks), Jan. 27, 1913, but refused; further roentgen-ray treatment at Boston City Hospital and Boston Homeopathic Hospital; no improvement; referred to Dr. Coley April 7, 1913; toxins 3 weeks; no improvement; amputation; prolonged toxins afterward (Coley)	Recovery	Well 12 years later
Very cellular, infiltrating, small cell sarcoma, probably periosteal (Ewing); revised diagnosis: endothelioma (Ewing)	Few weeks.....	Exploratory operation (Hoguet and Coley); toxins and radium (Coley), 90,000 millicurie hours radium at 6 cm. distance	Almost complete disappearance of tumor; September, 1920, evidence of metastases in liver; grew worse rapidly	Died, Dec. 14, 1920
Sarcoma	7 months.....	Amputation (Dr. R. W. Lovett of Boston), July, 1908; referred to Dr. Coley for toxins after operation; toxins given 2 to 3 times a week from July to October; highest dose 5½ minims; temperature 104.5 F.	Recovery	Patient well, 1924, 16 years later
Round cell sarcoma of radius; ulna tumor showed giant cells not in primary tumor	4 months.....	First operation: resection of humerus (Dr. H. Lilienthal) September, 1913; in May, 1914, developed tumor in ulna; typical roentgenogram of giant cell sarcoma; 9 doses of toxins; amputation (Dr. Lilienthal) November, 1914	Developed lung metastases	Died, December, 1913
Small round cell sarcoma	Swelling 5 months	Total excision of clavicle by Dr. Maurice H. Richardson; patient referred to Dr. Coley for prophylactic toxins; treatment kept up several months	Recovery	Well, June, 1925, 17 years later
Round cell sarcoma (Ewing)	Few weeks.....	Total excision clavicle (Coley) followed by prophylactic toxin treatment 3 to 4 months	Recovery	Well 15 years later
Endothelioma (Ewing)	2½ months.....	Immediate total excision clavicle; buried radium, bare tubes, in wound (8 millicuries) at time of operation	Wound sloughed some at site of buried radium; toxins begun 2 weeks after operation; kept up until August, 1924	Early in August noticed local return; massive dose of radium; toxins continued; gradual increase in size; died, Nov. 28, 1924
Periosteal osteogenic sarcoma (Ewing and Mallory)	8 months.....	Four operations by Dr. Frederic K. Lund of Boston; 2 radium treatments; referred to Dr. Coley, August, 1917; apparent recurrence at time toxins were begun; injections kept up 1 year; three roentgen-ray treatments	Recovery; no further recurrences	Patient well, July, 1926, 9 years later
No biopsy	3 months pain and swelling	Toxins and radium for nearly 1 year; gradual decrease in size of tumor and replacement of destroyed area with new bone	Complete recovery	Well, January, 1925, 7¾ years
Fibrosarcoma (New York Hospital laboratory)	Few months.....	Amputation (Dr. W. T. Bull), 1893; recurrence in stump and popliteal space 1½ years later; treated with toxins (Coley); great improvement; 2 inch (5 cm.) amputation; later increase in swelling; second amputation (Coley); recurrence; large inoperable tumor in gluteal region; incomplete removal; toxins resumed	Remainder of tumor absorbed	Patient well, January, 1925, 32 years after first operation

TABLE 7.—*Group I: Patients Treated by Toxins or*

Case	Date	Age	Sex	Locality	Trauma	Clinical Diagnosis	Roentgen-Ray Diagnosis
110	1906	24	♀	Metatarsal bone	?.....	Periosteal sarcoma	None.....
111	1912	12	♂	Clavicle.....	Fell, striking on wood box, 1 week before	Periosteal sarcoma	Periosteal sarcoma

TABLE 7.—*Group II: Patients Treated*

Case	Date	Age	Sex	Locality	Trauma	Clinical Diagnosis	Roentgen-Ray Diagnosis
112	October, 1923	17	♀	Femur, lower end	Fell down stairs, injuring right knee, 10 months before	Periosteal sarcoma	Periosteal sarcoma
113	February, 1924	22	♀	Femur, lower end	Severe blow, August, 1923; pain and swelling 2 months later	Periosteal sarcoma	Periosteal sarcoma
114	November, 1915	18	♂	Femur, midshaft	Strain 1½ years before; swelling for months later	Periosteal sarcoma	Periosteal sarcoma
115	September, 1922	34	♂	Femur, midshaft	Slight local trauma August 15; pain and swelling soon after	Periosteal sarcoma	Periosteal sarcoma
116	March, 1919	33	♀	Femur, lower end	None.....	Periosteal sarcoma	Appearance suggestive of giant cell sarcoma
117	February, 1924	22	♂	Femur, lower end	Struck thigh above knee September, 1923; pain 2 months, swelling 3 months	Periosteal sarcoma	Periosteal sarcoma
118	October, 1922	20	♂	Femur, upper third shaft	None.....	Periosteal sarcoma	Periosteal sarcoma
119	July, 1922	13	♀	Femur, midshaft	None.....	Periosteal sarcoma	Periosteal sarcoma
120	August, 1922	25	♀	Femur, lower end	Struck above knee, November, 1921; pain followed swelling in 2 months	Periosteal sarcoma	Periosteal sarcoma
121	September, 1924	19	♀	Femur, lower end	None.....	Periosteal sarcoma	Periosteal sarcoma
122	March, 1923	48	♀	Femur, lower end	Fell injuring knee 13 months before; had had pain before; swelling 1 month later	Central sarcoma, giant cell; central sarcoma, malignant (Coley)	Giant cell sarcoma...
123	January, 1923	25	♂	Femur, upper end	?.....	Central tumor, giant cell	Benign, giant cell sarcoma
124	January, 1924	14	♂	Femur, lower end shaft	None.....	Periosteal sarcoma	Periosteal sarcoma
125	February, 1922	31	♀	Femur, lower end	Fell down stairs 4 years before	Periosteal sarcoma	Periosteal sarcoma

Radium and Toxins or Amputation and Toxins—Continued

Microscopic Diagnosis	Duration	Treatment	Immediate Result	Final Result
Small round cell sarcoma (Ewing)	Few months.....	Exploratory incision; amputation of leg, middle and lower third; prolonged toxins after amputation	Recovery	Well 12 years later
Round cell sarcoma	1 to 2 weeks.....	Total excision clavicle (Coley)	Recovery; toxins for 2 to 3 weeks; recurrence 6 weeks later; rapid growth	Developed metastases and death occurred within 5 months from date of injury

with Radium and the Roentgen Rays

Microscopic Diagnosis	Duration	Treatment	Immediate Result	Final Result
No biopsy	2 months; pain and swelling first symptom	High voltage roentgen rays, 3 treatments, November 3 to 11	Nov. 3, 1923, no evidence of metastases; November 26, acute fulminating metastases; temperature 104 F.	Died Feb. 9, 1924; total duration of disease 5½ months
Osteogenic sarcoma	4 months.....	High voltage roentgen rays, Memorial Hospital; bony metastases in muscle of outer part of axilla removed; proved to be osteogenic sarcoma; amputation advised but refused	Grew thin and emaciated	Died
Round cell sarcoma	1 year; swelling first symptom	Treated at Bellevue Hospital (Dr. J. B. Bissell) with radium, after 10 doses of toxins; Dr. Coley advised amputation, refused	Severe deep burns; tumor apparently entirely disappeared; recurred locally 3 years later; general metastases	Further radium treatment; no effect; died, March 1919
Cellular giant cell tumor (Ewing); biopsy specimen after amputation diagnosed as malignant osteogenic sarcoma (Ewing)	1 month; pain and swelling	Radium from Sept. 9 to Nov. 3, 1922 (209,387 millicurie hours), largest dose used at Memorial Hospital	Disease not controlled; amputation, Dec. 10, 1922 (Dr. Quick)	Died few months later
Fibrosarcoma	1 year pain; 6 months swelling	Radium, March, 1919, to 1920; roentgen rays, May, 1921, to September, 1921	Disease controlled for nearly 4 years, then pathologic fracture	Amputation early in 1924; well 1½ years after amputation
Malignant osteogenic sarcoma	3 months.....	Roentgen rays 2 months; swelling and pain increased; amputation (Coley), May 20, 1924; toxins for nearly year	Recovery; no recurrence	Well nearly 2½ years after amputation
No biopsy	2 months; first symptom swelling; pain soon after	High voltage roentgen rays, October, 1922; no improvement; radium, bare tubes (78 millicurie hours) in tumor; total, 10,236 millicurie hours	No improvement; tumor increased in size; rapid loss of strength and flesh	Died few months later
No biopsy	5 months, pain and disability; tumor 3 months	Roentgen rays July, 1922, to January, 1923	Definite increase in density; slow increase in size; December, 1922, clinical evidence of lung metastases	Grew worse and died in February, 1925
No biopsy	7 months; pain first symptom	Sixteen electrical treatments elsewhere; 6 roentgen-ray treatments at Memorial Hospital, August to November, 1922	No improvement; amputation advised; took high voltage roentgen rays at another hospital; no improvement; amputation early in 1924	Well 1 year later
.....	Pain 2 months; tumor 6 weeks	Six roentgen-ray treatments at Memorial Hospital, Sept. 12 to Oct. 20, 1924; readmitted, Dec. 2, 1924	Severe pain not controlled by roentgen rays; steady increase in size; great increase between October 24 and December 2; much emaciated	Amputation, Dec. 9, 1924
Giant cell sarcoma from gross appearance of tumor and biopsy; microscopic examination after amputation: malignant large spindle cell sarcoma (Ewing)	Pain 12 months; tumor 10 months	Plaster cast for several months; later radium and roentgen rays; exploratory operation 6 months before admittance to Memorial Hospital; amputation (Dr. Martin) March 16, 1923	Recovery	Lung metastases; died few months later
No biopsy at first; 8 months later curettage; diagnosis: degenerating chondroma (Ewing)	.....	Treated with roentgen rays 6 months at Memorial Hospital; slow increase; curettage (Coley), August, 1923; very vascular, red, pulpy tissue closely resembling giant cell tumor	Tumor continued to grow; condition beyond hip joint amputation; great pain; loss of weight	Died of exhaustion, August, 1924
No biopsy	Pain 3 years; tumor soon after	Eleven high voltage roentgen-ray treatments, February to August, 1922	Disease not controlled; Oct. 21, 1922, amputation advised	Not traced
No biopsy	2 months; severe pain first symptom	Four high voltage roentgen-ray treatments (80 minutes each), January to March, 1924	Marked improvement; disease apparently under control, December, 1924	Not traced

TABLE 7.—*Group II: Patients Treated with*

Case	Date	Age	Sex	Localtiy	Trauma	Clinical Diagnosis	Roentgen-Ray Diagnosis
126	May, 1915	10	♂	Femur, midshaft	Fell on steel rail injuring midthigh; swelling 2 months	Periosteal sarcoma	Periosteal sarcoma
127	January, 1916	21	♂	Femur, lower third	None.....	Periosteal sarcoma	Periosteal osteosarcoma
128	February, 1922	18 colored	♂	Femur, midshaft	Kicked in midthigh July, 1921; local pain 2 months; swelling soon after	Periosteal sarcoma	Periosteal sarcoma
129	June, 1923	13	♀	Femur, lower end	None.....	Periosteal sarcoma	Periosteal sarcoma
130	March, 1921	30	♂	Femur, shaft.....	Severe blow, anterior thigh, by barrel of molasses, Nov. 13, 1920; pain few days later; lump, size of fist, soon after	?..... (Case of Drs. Quick and Cole)	Periosteal sarcoma (Dr. Rufus Cole)
131	June, 1923	42	♂	Femur, shaft.....	Fall from car 7 months before; lump appeared 2 months after	Periosteal sarcoma ?	Osteogenic sarcoma; suggested slowly growing and benign type
132	December, 1924	21	♀	Femur, lower end	Six months before, struck knee on footpress; swelling noticed immediately after	Periosteal sarcoma	Osteogenic sarcoma
133	January, 1925	14½	♀	Femur, lower third	No history of trauma	Periosteal sarcoma	Osteogenic sarcoma, distal third of femur, Jan. 20, 1925
134	February, 1925	53	♂	Tibia, upper end	?.....	Central sarcoma, clinically malignant	Central sarcoma, giant cell
135	March, 1922	15	♂	Humerus, upper third	Fell from sled injuring arm 7 weeks before; had had pain 1 week before injury	Periosteal sarcoma	Periosteal sarcoma
136	April, 1921	31	♀	Humerus, lower end	None.....	Periosteal sarcoma	Roentgen ray showed no bone involvement
137	August, 1920	44	♀	Humerus, middle and upper third of shaft	None.....	Periosteal chondrosarcoma	Enchondroma, benign
138	July, 1920	23	♂	Humerus, midshaft	None.....	Periosteal sarcoma	Periosteal sarcoma
139	1924	15	♂	Humerus, upper end	None.....	Giant cell tumor ?...	Chrondrosarcoma ?
140	April, 1918	70	♀	Humerus, upper midshaft	None.....	Periosteal sarcoma	Sarcoma.....
141	October, 1923	40	♂	Humerus, upper end	None.....	Periosteal sarcoma	Periosteal sarcoma
142	1922	14	♂	Humerus, upper third	Local injury.....	Periosteal sarcoma	Periosteal sarcoma
143	1915	51	♂	Humerus, upper third	None.....	Sarcoma.....	Sarcoma.....
144	January, 1922	24	♀	Humerus, upper third	None.....	Probable sarcoma...	Osteosarcoma of medullary origin

Radium and Roentgen Rays—Continued

Microscopic Diagnosis	Duration	Treatment	Immediate Result	Final Result
Round cell sarcoma	4 months.....	Radium, Memorial Hospital.....	Reduced to one third original size; spontaneous fracture; September 1915, entered New Haven Hospital	Amputation; lung metastases; died few months later
No biopsy	2 months.....	Radium, Memorial Hospital (Dr. H. H. Janeway), July to September, 1916	Improved at first; later slight enlargement; general condition grew worse	December, 1916, lung metastases; died shortly after
No biopsy	3 months.....	Roentgen rays from March 11 to Aug. 14, 1922	Sept. 11, 1922, evidence of lung metastases noticed	Died, Sept. 20, 1922
No biopsy	2 months pain.....	Two roentgen-ray treatments, June 25 to 29, 1923	.....	Not traced
No biopsy	9 months.....	Roentgen-ray treatment (Dr. Cole), December, 1920, to March, 1921; radium bare tubes buried in tumor at Memorial Hospital (Dr. D. Quick)	Swelling disappeared	Well, December, 1924; clinical history favors diagnosis of myositis ossificans
No biopsy	5 months.....	Three high voltage roentgen-ray treatments, June, 1923, to December, 1923	Improvement	Not traced
Osteogenic chondrosarcoma (Ewing)	6 months.....	High voltage roentgen-ray treatmen for 1½ months, until Feb. 19, 1925	Increase in pain and swelling; amputation, March 11, 1925	Metastases one lung 4 months later
None	Pain 4 months; swelling 1 month	Two roentgen-ray treatments before coming to Memorial Hospital; roentgen-ray treatments: Jan. 26, 1925, to chest; January 31, to chest; February 4 to March 26, 7 (80 minutes each) to femur; March 27, 35 minutes; March 30, 80 minutes; March 31, 45 minutes; April 7, 80 minutes; May 27, 60 minutes; June 3, 60 minutes	Feb. 28, 1925, evidence of considerable increase in size of tumor; no evidence of metastases in lungs; May 18, considerable increase in ossification of tumor; appeared definitely encapsulated	Feb. 28, 1925, roentgenogram of chest revealed evidence of large metastatic tumors; died shortly after
Biopsy: malignant osteogenic central sarcoma (Ewing)	Few months; June, 1925, large, fungating tumor	Roentgen-ray treatment for 4 months; disease not controlled; general condition deteriorated; evidence of abdominal metastases	Amputation early in July, 1925, as palliative measure (Dr. Verdi, New Haven); recovery from operation (Note: This patient was not treated by us but was seen in consultation)	Well 1 year later
Osteogenic periosteal sarcoma	3 to 4 months.....	Radium	Steady increase in size...	Died
Large, spindle cell, osteogenic sarcoma, periosteal	6 months pain.....	Radium pack 4 months (Dr. D. Quick), 85,000 millicurie hours	Steady increase in size; amputation, October, 1921 (Quick)	Reported well, October, 1924 (Dr. Quick)
Soft chondroma; rather numerous cells, large spindle, about lobules of cartilage	3 years pain; 2 years tumor	Treated 3 years for neuritis; Memorial Hospital treatment: radium (44,864 millicurie hours) and roentgen rays (14 treatments)	Little effect in tumor; steady increase in size	Further intensive roentgen-ray treatment after leaving Memorial Hospital; died of exhaustion July, 1923
Fibro-endothelioma, not essentially malignant	1 year.....	Radium (40,027 millicurie hours); disease not controlled; amputation, October, 1920	Metastases in lung 5 months after amputation	Died soon after
No biopsy	6 months pain.....	Eight doses toxins; radium, 88,000 millicurie hours	No increase in tumor; general condition good; 10 months later	In good condition, August, 1925
No biopsy	6 months pain.....	Had 8 doses Coley's toxins, then treated with radium, 8 treatments (88,000 millicurie hours)	Great improvement; in good condition nearly 2 years; then grew worse	Probable metastases; died July, 1920
.....	6 months pain; 4 months swelling	Local operation, July, 1923; high voltage roentgen rays, October, 1923, to January, 1924; steady increase in size; March 1, 1924, fungating tumor removed with cautery (Dr. Stone)	Interscapular thoracic amputation (Dr. Adair); recovery	In hopeless condition, September, 1925; died shortly after
Telangiectatic sarcoma (Ewing)	Few months.....	Roentgen rays 4 months; increase in size; amputation, January, 1922 (Dr. B. L. Coley)	Recovery	Well, December, 1924
Small spindle cell sarcoma (Larkin)	Paralysis 2½ years before	Roentgen rays; resection head of humerus, head of scapula and outer end of clavicle (Dr. N. W. Green)	Recovery	Well 9 years later; resection was for an old roentgen-ray burn that would not heal; the sarcoma was discovered on microscopic examination of specimen
No biopsy	Pain 6 months; tumor soon after	Roentgen-ray treatment, 9 exposures from January to March, 1922	Slight improvement	Not traced

TABLE 7.—*Group II: Patients Treated with*

Case	Date	Age	Sex	Locality	Trauma	Clinical Diagnosis	Roentgen-Ray Diagnosis
145	April, 1918	44	♀	Humerus, upper end	None.....	Periosteal sarcoma	Periosteal sarcoma
146	July, 1918	19	♂	Humerus, lower end	Fracture 2 years before	Periosteal sarcoma ?	Probable sarcoma...
147	February, 1919	27	♂	Humerus, upper end	None.....	Periosteal sarcoma	Periosteal sarcoma ?
148	February, 1919	19	♂	Humerus, upper end	Local injury in 1918; pain and swelling soon after	Periosteal sarcoma	Periosteal sarcoma
149	November, 1924	13	♀	Humerus, upper end	?.....	Periosteal sarcoma	Periosteal sarcoma
150	February, 1918	33	♀	Humerus, upper end	Local injury; pain 6 months later	Chondrosarcoma....	Sarcoma.....
151	March, 1920	15	♂	Humerus, middle	Recent fracture.....	?.....	?.....
152	October, 1924	13	♀	Tibia.....	Local trauma.....	Periosteal sarcoma	Periosteal sarcoma
153	December, 1923	13	♂	Tibia, upper end	Injured shin diving off springboard, August, 1923; pain 3 to 4 weeks later; tumor 2 months after injury	Periosteal sarcoma	Periosteal osteogenic sarcoma
154	July, 1922	27	♂	Tibia, upper end	Fell downstairs, wrenching leg; tumor 1 week later	Periosteal sarcoma	Periosteal sarcoma
155	June, 1922	35	♀	Tibia, upper end	Local injury, May, 1920, also June, 1920, and May, 1921; tumor 6 weeks after last injury	Central sarcoma, giant cell ?	Giant cell sarcoma...
156	July, 1922	41	♀	Tibia, shaft.....	None.....	Periosteal sarcoma	Periosteal sarcoma
157	October, 1923	8	♂	Fibula, lower end	None.....	Bone abscess.....	Alteration in density not suggestive of osteosarcoma; "trophic osteitis"

Microscopic Diagnosis	Duration	Treatment	Immediate Result	Final Result
No biopsy	Pain 2 years; tumor more than 1 year	Massage and osteopathy for several months; 11 months before had radium in Baltimore	Little improvement; had huge inoperable tumor when admitted to Memorial Hospital; received palliative radium treatment	Died, Dec. 5, 1918
Osteosarcoma, probably periosteal (Ewing)	Tumor 3-4 years; began to grow 9 months before examination	Local excision, February, 1918, encapsulated tumor attached to periosteum, outer condyle; prophylactic radium at Memorial Hospital (21,000 millicurie hours), March, 1918	?	Not traced
Osteochondrosarcoma	Pain and disability following typhoid inoculation 1½ years before; treated 1 year for neuritis	Operation, Jan. 21, 1919, New York Hospital (Dr. Hitzrot); resection upper 4 inches (10.1 cm.) of bone; bone graft implanted; referred to Memorial Hospital, February, 1919	Treated with radium pack 3 months (85,000 millicurie hours); roentgen-ray examination, April and May, showed recurrence of disease	Gradually returned to normal; patient well, June, 1925, 6 years later
Osteogenic sarcoma; chondrosarcoma structure shows mostly cartilage	6 months.....	Radium treatment (60,250 millicurie hours) by Dr. Janeway, February and March, 1919	Tumor steadily increased in size; very large in October, 1919, when Dr. Matthews, at St. Luke's Hospital, did interscapular thoracic amputation	Died; lung metastases 5 months later
Osteogenic sarcoma	7 months.....	Treated with roentgen rays at Mt. Sinai Hospital 6 weeks after first noticed; amputation advised but refused; roentgen rays continued; admitted to Memorial Hospital November, 1924; amputation advised but refused	Palliative treatment; given; lungs free	Died few months later
Chondroma (February, 1918); chondrosarcoma (May, 1919)	1 year.....	Local operation, June, 1917; amputation advised by several surgeons; treated at Memorial Hospital with radium pack (10 treatments) and bare tubes (7 treatments, 9 to 37 millicurie hours) from Feb. 8, 1918, to Aug. 8, 1919	Marked improvement; large tumor nearly disappeared; recurred and no longer favorably affected by resection	Died early in 1920
Myxosarcoma	Few weeks.....	Operation 1 month after fracture; roentgen rays and radium (9,790 millicurie hours), March 25, 1920	Recovery	Well 3 years later
Osteogenic sarcoma (Ewing)	2 months.....	Roentgen-ray treatment 4 weeks; amputation followed by toxins	Recovery	Metastases in lung and large recurrence in stump of thigh 8 months after amputation; condition very far advanced; huge tumor and condition regarded as hopeless when patient first came under our observation
Chondrosarcoma .	2 months.....	Dec. 19 to 22, 1923, 48,000 millicurie hours radium (pack) at 10 cm. distance; Feb. 15 to 18, 2 exposures high voltage roentgen rays, 80 minutes (Dr. D. Quick)	Tumor not controlled; amputation performed, March 17, 1924	Metastases in 2 to 3 months; died
Spindle cell periosteal sarcoma	1½ years.....	Radium, 50 millicurie hours, bare tubes in tumor Aug. 3, 1922; radium packs (78,916 millicurie hours) from July, 1922, to Jan. 24, 1923	Steady increase in size of tumor; amputation by Dr. B. L. Coley	
Gross diagnosis: telangiectatic osteogenic sarcoma, aneurysm of bone with giant cell reaction (Ewing)	1 year.....	Radium pack (6,240 millicurie hours), June, 1923; 13 injections toxins, June, 1922; 3 high voltage roentgen-ray treatments, June, 1922, to January, 1923	Steady increase in size; increase in bone formation; pathologic fracture; leg useless, October, 1923, to June, 1924; amputation at thigh June 5, 1924 (Coley), followed by toxins	Well, December, 1924; August, 1926, general condition poor; no definite evidence of metastases
Alveolar sarcoma, periosteal	Swelling of tibia 2 years before; 2 years later local removal; local recurrence 5 years before; second local removal, April, 1922, by Dr. Parker; recurrence, July, 1922, with metastases in lungs	Roentgen-ray treatment at Memorial Hospital July, 1922, to January, 1923, 9 treatments; further treatment in 1924	Local condition controlled; metastases in lung held quiescent for 2 years; general condition good	December, 1924, general condition good; lung metastases getting larger; April, 1926, general condition much worse
Structure indicates slowly growing, sclerosing type of osteogenic sarcoma	Pain 3 years; swelling soon after; no treatment until July, 1923	Oct. 12, 1923, 1 roentgen-ray treatment	No change	In good condition, December, 1924

TABLE 7.—*Group II: Patients Treated with*

Case	Date	Age	Sex*	Locality	Trauma	Clinical Diagnosis	Roentgen-Ray Diagnosis
158	December, 1920	17	♂	Tibia, upper shaft	None.....	Sarcoma.....	Proliferation of periosteum; medullary canal somewhat expanded
159	May, 1922	65	♂	Tibia, upper half of shaft	None.....	Osteomyelitis; periostitis (Bloodgood); Paget's disease; subperiosteal, nonsuppurating periostitis	Osteitis or osteomyelitis
160	September, 1922	18	♀	Tibia, shaft.....	Fall 7 months; local injury head of tibia; tumor 2 months	Osteomyelitis (Hospital for Ruptured and Crippled)	Lacks appearance usually noted in periosteal or giant cell growths; diagnosis: endothelioma (Herendeen)
161	March, 1921	44	♀	Tibia, upper end	None.....	Central sarcoma.....	Giant cell tumor.....
162	June, 1919	19	♂	Tibia, upper end	None.....	Central sarcoma.....	Benign giant cell sarcoma
163	November, 1919	14	♀	Radius, shaft.....	Strain, November, 1918; swelling next day at site of injury; second injury, July, 1919; tumor next day persisted	Periosteal sarcoma	Sarcoma.....
164	May, 1919	40	♂	Ulna, shaft.....	Frequent strain from cranking car	Periosteal sarcoma	Periosteal sarcoma
165	March, 1916	37	♂	Radius, lower end	Sprain 4 years before; tumor soon after slowly increased in size	Periosteal sarcoma	Periosteal osteosarcoma
166	March, 1920	12	♀	Clavicle, inner end	None.....	Periosteal sarcoma	Periosteal sarcoma
167	March, 1921	30	♀	Clavicle, inner end	None.....	Sarcoma.....	Destructive process inner end clavicle and sixth cervical vertebra simulated endothelioma
168	October, 1923	9	♂	Os calcis.....	None.....	Endothelioma.....	.....
169	1918	Adult	♂	Clavicle.....	?.....	Sarcoma.....	Sarcoma.....
170	April, 1924	23	♀	Tibia, upper end	None.....	Osteogenic sarcoma	Osteogenic sarcoma
171	March, 1925	21	♀	Tibia, lower end	?.....	Giant cell tumor.....	Giant cell tumor.....

Microscopic Diagnosis	Duration	Treatment	Immediate Result	Final Result
Endothelioma (Ewing), perithelial growth in dense scar tissue	Pain 1 year; swelling 1 month	Radium pack, December, 1920, to May, 1923 (101,181 millicurie hours), also roentgen-ray treatments	Improvement; disease controlled for nearly 3 years, then signs of activity; amputation, November, 1923	Well 1 year later
No biopsy; chondrosarcoma (Ewing)	4 months, severe constant pain	Removal of teeth; roentgen-ray treatment, May, 1922; amputation at thigh, August, 1922	Pain and disability increased and became very severe	Died of lung metastases 2 months later
No biopsy	Pain 5 months; swelling later	Roentgen rays, September to December, 1922, 6 treatments (Herendeen)	Marked improvement	Well, December, 1924
Giant cell tumors, epulis type	4 months.....	Curettage, New York Hospital, October, 1920; second operation, March, 1921; 32 millicurie hours bare tubes and 222 millicurie hours silver tubes radium; several radium pack and bare tube treatments at Memorial Hospital	Disease not controlled; amputation at Presbyterian Hospital, October, 1921; recurrence in thigh stump 6 months later	Further roentgen-ray treatments; died in 1922 of extension of metastases in pelvis
Benign giant cell sarcoma (Ewing, Bloodgood, Mallory, Codman); osteogenic sarcoma with giant cells, malignant (Wood)	5 months pain.....	Curettage, Dr. Walton Martin, June, 1919; referred to Memorial Hospital after operation, June 28, 1919; treated with radium, bare tubes (2,256 millicurie hours) unfiltered radium	Cavity slow in healing but no infection until April, 1920, when recurrence was noticed; second curettage infection; amputation (Coley), June 9, 1920	Developed metastases in both lungs, February, 1921; died 2 months later
Endothelioma; endothelial myeloma (Ewing)	4 months.....	Small doses of toxins at Mt. Sinai Hospital for 2 weeks; admitted to Memorial Hospital Nov. 25, 1919; radium, December to November, 1920 (11,298 millicurie hours), pack at 6 cm. distance	Almost complete disappearance of tumor in few weeks; August, 1920, arm normal; September, 1920, recurrence; metastases rapidly developed	Died, January, 1921; much emaciated; skull studded with tumors
Osteogenic sarcoma	Few months.....	Radium at Memorial Hospital (Dr. D. Quick) from May to October, 1919	Steady increase in size; amputation at St. Luke's Hospital (Dr. Schley), Oct. 27, 1919	Metastases 3 months later; died
"Sarcoma" (at another hospital)	4 years.....	Excision 3 months before at another hospital; local recurrence; treated with radium at Memorial Hospital (Dr. Janeway) 18,918 millicurie hours at 3 cm. distance in lead plaques, 3 mm. lead filter	Superficial burns; little effect on tumor; amputation advised	Returned to Italy; not traced
No biopsy	1 month.....	Radium pack (30,156 millicurie hours), radium bare tubes (17 millicurie) by Dr. D. Quick; 7 roentgen-ray treatments	Marked improvement; tumor nearly disappeared; recurrence in 3 months	Died Jan. 20, 1920; total duration of disease, 6 months
Small, round, polyhedral cells show features of endothelial cells but not typical of endothelioma, may be myeloma or epithelioma	9 months.....	Radium (32,670 millicurie hours) at 6 cm. distance	Recovered from paralysis; tumor disappeared	Well 2 years; death, June, 1925, possibly due to metastases
Endothelioma	1 year.....	Radium (48,000 millicurie hours) at 6 cm. distance; roentgen rays from Oct. 3, 1923, to May 6, 1924	Some improvement; later pain and swelling increased; metastases	Died, May 14, 1924
Myeloma	.....	Excision of clavicle by Dr. Hitzrot at New York Hospital; local recurrence	Treated at Memorial Hospital with radium (Dr. Quick); disease not controlled	Died 6 months later from what we believe to be lung metastases
No biopsy	4 months.....	Roentgen-ray treatment at Memorial Hospital (Herendeen)	Steady but slow increase in size, increased more rapidly last few weeks; very much new bone production	Under treatment
No biopsy	Swelling immediately after injury	Roentgen-ray treatment at Memorial Hospital from April 20 to Sept. 20, 1925	Condition gradually getting worse	Metastases in lungs, September, 1925

* In this table, ♂ indicates male; ♀, female.

thirty-nine years later. Of these thirty-eight patients, twenty were treated with toxins alone (the limb saved in eight cases) and eighteen were treated with toxins and radium (the limb saved in eleven cases).

TABLE 8.—*Patients with Periosteal Osteogenic Sarcoma, Including Endothelioma, Well Five Years Plus*

Case	Locality	Treatment	Results
1	Tibia	Toxins alone	Well 27 years; limb saved
2	Humerus	Toxins alone	Well 24 years; limb saved
3	Femur	Toxins alone for extensive metastases after failure of roentgen rays	Well 11 years; limb saved
4	Femur	Amputation and toxins	Well 17 years
5	Femur	Amputation and toxins	Well 16 years
6	Humerus	Toxins, amputation, toxins	Well 8 years; then died of lung metastases
7	Femur	Toxins alone	Well 12 years; limb saved
8	Femur	Toxins and radium	Well 5 years; limb saved
*9	Femur	Toxins alone	Well 13 years; limb saved
10	Humerus	Toxins and roentgen rays	Well 15 years; limb saved
11	Tibia	Toxins and radium (clinic and roentgen-ray diagnosis)	Well 6 years; limb saved
12	Femur (inoperable)	Toxins and radium	Well 8 years; limb saved
13	Clavicle	Excision and toxins	Well 15 years
14	Clavicle	Excision and toxins	Well 16 years
15	Femur	Toxins, radium, amputation, toxins six months	Well 8 years
16	Femur	Radium, toxins, amputations, toxins	Well 8 years
17	Tibia	Amputation and toxins	Well 8 years
18	Femur	Toxins, radium, amputation, toxins	Well 5½ years
19	Metatarsal bone	Amputation; recurrence; toxins	Well 30 years
20	Metatarsal bone	Amputation and toxins	Well 12 years
21	Femur	Toxins, amputation, toxins	
22	Radius	Roentgen rays, toxins, amputation, toxins	Well 16 years Well 13 years
23	Mastoid	(Four recurrences.) Radium; failure to control; toxins	Well 9 years
24	Rib	Toxins (clinical and roentgen-ray diagnosis)	Well 9½ years
25	Tibia with metastases in inguinal, iliac and femoral glands	Radium and toxins (2¼ years)	Well 9½ years
26	Femur	Toxins, radium, amputation, toxins	Well 9 years
27	Femur	Amputation and toxins	Well 18 years
28	Femur (inoperable); metastases in skull	Toxins and radium	Well 6¾ years
29	Fibula (inoperable); metastases in groin and lungs	Toxins 3 months; 1 radium treatment to groin	Well 5¾ years
†30	Humerus (inoperable)	Toxins	Well 7 years; limb saved
‡31	Femur	Toxins	Well 6 years; limb saved
§32	Femur (roentgen-ray and clinical diagnosis)	Toxins	Well 5 years

Limb saved in 15 cases

Microscopic examination in 26 cases (periosteal osteogenic sarcoma, 20 cases; endothelioma, 6 cases).

Cases in Which Clinical and Roentgen-Ray Diagnosis Was Made

1 Exploratory incision; typical periosteal sarcoma of femur
2 Beyond hip joint amputation; destruction of 5½ inches (13.9 cm.) of femur
3 Packard's case; inoperable, upper third of femur; child weak and emaciated when treatment was begun
4 Roentgen-ray and clinical diagnosis: probable endothelioma of tibia
5 Inoperable first rib; clinical and roentgen-ray diagnosis; sarcoma
6 Inoperable sarcoma of humerus, with metastases in lung

* Williamson's case. † Mackid's case. ‡ Wilmoth's case. § Packard's case.

CONCLUSIONS

1. The prognosis of osteogenic sarcoma of the long bones, while far from satisfactory, is by no means as hopeless as is generally believed by physicians.

2. The prognosis depends largely on an early diagnosis and the exercise of most careful judgment in selecting the method of treatment for the individual cases; this should be based on a wide experience with a great variety of clinical and pathologic types of bone sarcoma.

3. Amputation alone offers little hope of a permanent cure in any of these types.

4. Primary treatment with radium or roentgen rays, even if pushed to the utmost limits of safety, while often causing very marked improvement has thus far failed to effect a permanent cure in any case in which the diagnosis has been unquestionably established by clinical and pathologic evidence.

5. The mixed toxins of erysipelas and *Bacillus prodigiosus* alone have effected a cure in a certain number of cases; but all of these cases have been of the round cell or spindle cell type, characterized by little production of new bone.

6. The mixed toxins and radium combined have likewise resulted in the complete disappearance and apparent cure of an even larger number of cases of a similar type; but neither toxins nor radium, singly or combined, have effected a cure in any case associated with marked new bone production.

7. Amputation followed by prolonged treatment with the mixed toxins in a series of thirty-eight consecutive cases shows 50 per cent of the patients alive and well from three to eighteen years. This series includes all types of osteogenic sarcoma, as well as the cases associated with marked new bone formation.

8. In a similar series of cases treated by amputation alone without toxins or radium before or after amputation, not a single patient has remained alive beyond the three year period.

9. The choice of treatment in a given case depends on whether it belongs to the group of round cell sarcoma (endothelioma, according to Ewing's classification) or to the group associated with marked new bone formation. If to the first group, we believe it is safe to try a combination of the systemic effect of toxins and the local effect of radium, the duration of the treatment to depend on the result obtained; if marked improvement is noted, the treatment may be continued until the tumor has entirely disappeared; but if no improvement is noted in from four to six weeks amputation should be performed, followed by prolonged systemic toxin treatment.

If the case belongs in the second group, we see no advantage, but a distinct disadvantage, in preliminary treatment with radium, roentgen rays or toxins, for the reason that metastases may develop during the period of treatment or may be hastened by the rapid breaking down of a vascular tumor, which permits living cells to be carried to the lungs

or to remote parts of the body. As our experience, supported by the results of other men, shows that there is no reasonable hope of saving the limb in this group of cases, we believe that amputation at the earliest possible moment followed by prophylactic toxin treatment offers the greatest hope of saving the life of the patient.

10. The fact that ten inoperable cases of this series have been successfully treated with the mixed toxins alone or combined with radium, the patients remaining well from five to twenty-four years later, should prevent us from abandoning all hope in cases beyond surgical relief.

(To be continued)

TOTAL COLECTOMY AS A TREATMENT OF THE MEGASIGMOID; END-TO-SIDE ANASTOMOSIS *

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In a series of twenty-five partial resections of the sigmoid flexure (megasigmoid) including nine complicated cases,[1] I have noted during a period of from six months to two years a relapse in one fourth of the cases. Judging from this result, I conclude that in my hands partial colectomy for this condition has not been successful.

This failure may not cause any surprise because by means of the partial colectomy only the most altered portion of the colon is removed. The supralying and the infralying segments may transform themselves, in time, to an inert receptacle for feces. My attention was duly called to the fact that the recurrences among the noncomplicated cases with an emergency condition were noted in those cases in which a clinical picture of a left sided constipation predominated. Among the complicated cases, 50 per cent repeated "fecalomas" were registered in the history. The four reported patients with volvulus who had the sigmoid removed were cured permanently.

With this experience I decided to treat the left sided constipation, chiefly complicated in the fecaloma and when all treatments have failed, by means of total colectomy.

REPORT OF CASES

CASE 1.—*History.*—M. C. N., a woman, aged 27, married, a cook, was admitted to the surgical ward of the hospital de clinicas, Aug. 23, 1911. She had had five children. From her childhood she had been constipated. Toward the middle of 1921 a large fecaloma was removed from her.

Since some fifteen days before admission she had been unable to move her bowels even with purgative or enema. During the last few days she had complained from time to time of sharp abdominal pains. Gas was passed only with difficulty.

Physical Examination.—There was pronounced abdominal meteorism. Peristaltic waves were visible through the abdominal wall. By palpation a tumor the size of the head of a fetus could be felt over the pubis; it was embedded in the superior strait of the pelvis, of a pasty substance and pliable to pressure with the fingers.

The palpation of the abdomen was painful. It was found that the fecaloma occupied part of the pelvic cavity.

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* From the surgical department of University of Cordova Medical School.

1. Mirizzi: Colectomia de urgencia por megacolon ileo-pelviano complicado, Rev. Asoc. méd. argent., September, 1921, No. 203.

August 24, oil, soap and oxygenated water enemas were tried without any result whatever. There was vomiting and abdominal pain. The pulse, respirations and temperature were normal. The fecaloma had not changed.

August 25, an attempt was made to extricate the fecal accumulation with the hand, but it could not be reached. The general condition of the patient remained unchanged.

Operation.—August 26, a total colectomy[2] was performed, Dr. F. Olmedo assisting me. The operation lasted two hours and fifteen minutes. The first hour

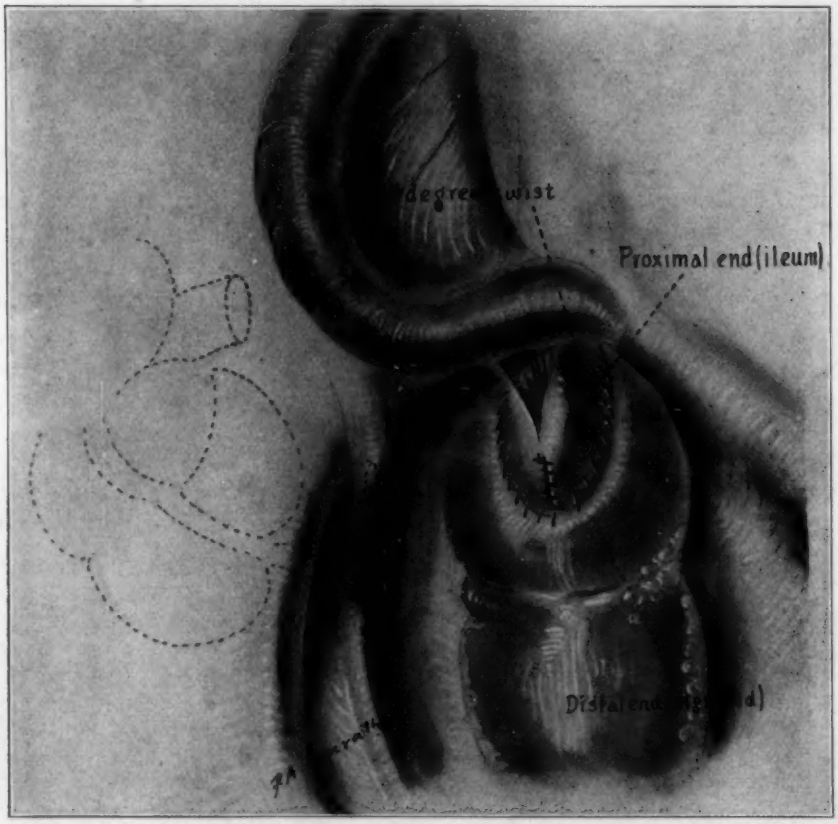

Fig. 1.—Side (of ileum) to end (of sigmoid) anastomosis, showing forward concavity and undesirable twist of 180 degrees.

and a quarter spinal anesthesia with stovaine-strychnine (Jonnesco) was used; the remaining forty-five minutes were under general anesthesia with ether, chloroform and oxygen (Roth-Drager apparatus).

A midline incision, 4 inches (10.1 cm.) above and below the umbilicus, was made. An enormous sigmoid flexure with a large amount of fecal contents was easily brought out. The operation was carried on by a careful separation of the

2. Strictly speaking, a total colectomy never is carried out owing to the fact that the anus, rectum and a few inches of the distal sigmoid flexure are left in place.

omentum from the transverse mesocolon (Lardennois-Okinczyc); easy loosening of the right and left colic angles, ascending, descending and sigmoid flexure. The hemostasis was easily accomplished by six ligations. The ileum was cut 5 cm. from the Bauhin valve with the cautery; the sigmoid was cut a few inches above the rectum with the scalpel and the end was touched with 5 per cent tincture of iodine. The end of the ileum was closed according to the De Martel procedure. A side opening was made in the ileum (9 cm.) in order to make an anastomosis with the colon (side-to-end anastomosis). The end of the ileum brought in contact with the distal opening[3] described a forward concavity. Near the anastomosis was noted a twisting of the ileum of 180 degrees around its longitudinal axis (fig. 1). In view of the obstruction caused by this abnormal location of the ileum, the anastomosis was undone, being fixed in the manner indicated in the paragraph relating to the technic of so-called side-to-side anastomosis, that is to say, with the loop of the ileum describing an anterior convexity. By doing this the proximal portion was drawn in contact with the posterior border (mesosigmoid) of the distal portion (fig. 2). Waxed linen thread was used in three rows of continuous sutures. Drainage through the anastomosis with a Faucher rubber tube was established through the anus.

The postoperative period was quiet and the patient made an uneventful recovery, leaving the hospital twenty days later.

This patient was examined in January, 1925, and was pregnant and perfectly well, having three or four stools daily. Lately, I learned that she gave birth to her child and is enjoying good health.

CASE 2.—*History.*—A. S., a married woman, aged 26, an Argentinian, entered the surgical ward of the hospital de clinicas, Sept. 14, 1922.

She had had whooping cough, smallpox and measles during childhood, and constipation for the last ten years. Lately two fecalomas were extracted.

Since one month before admission she had not been able to move her bowels, either with purgative or with enemas; she suffered general discomfort and sometimes sharp pain in the abdomen.

Physical Examination.—Information obtained by abdominal and rectal examinations demonstrated an enormous amount of feces in the distal portion of the colon. During the days following her admission the colon was emptied by means of enemas and manually.

Operation.—September 23, I performed a total colectomy, Dr. F. Olmedo assisting me. The operation lasted two hours under general anesthesia with ether, chloroform and oxygen (Roth-Drager apparatus). A midline incision was made. The easy separation of the transverse mesocolon from the omentum, as described by Lardennois and Okinczyc, was this time difficult; the left colic angle was troublesome to detach; hemostasis was obtained with five ligations; the ileum was cut 5 cm. above the Bauhin's valve by cautery; the sigmoid flexure was separated as near as possible to the rectum with the scalpel and immediate application of 5 per cent tincture of iodine was made.[4] The proximal end (ileum) was stitched up according to De Martel. Anastomosis was accomplished with three rows of continuous suture, using waxed linen thread. The anastomosis was made as shown in figure 2, and rubber tube drainage was instituted through the anastomosis.

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3. For a better understanding, the end of the ileum and its lateral opening will be called proximal and the end of the sigmoid will be called distal.

4. The diameter of the distal opening (colon) measured 10 cm.

During the days after the operation no noteworthy incident occurred. The patient was allowed to leave the hospital eighteen days later, completely cured.

According to the latest news received from her, August, 1925, she feels perfectly well and her bowels evacuate three times a day.

Case 3.—*History.*—R. L., an unmarried woman, aged 40, entered the surgical department of the hospital de clinicas, Nov. 11, 1922. She had had smallpox,

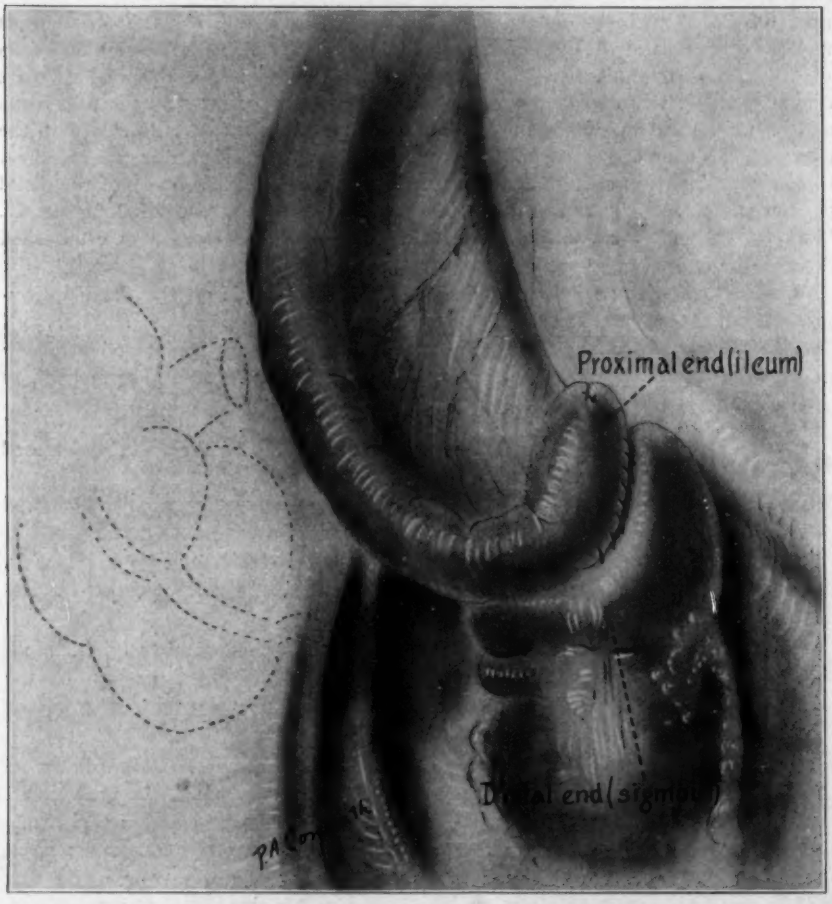

Fig. 2.—Side (of ileum) to end (of sigmoid) anastomosis, showing anterior convexity which is the position desired to avoid the twist of 180 degrees.

whooping cough and measles between 5 and 9 years of age, and had had constipation from childhood. On admission she had had no stool for a month.

Physical Examination.—She had chronic bronchitis and meteorism. At the clinic it was noted that the sigmoid flexure and the rectum were the seat of a large fecaloma. During the following days by enemas and manually the colon was emptied.

Operation.—November 30, as the patient was in fairly good general condition, I operated, assisted by Dr. F. Olmedo. Chloroform anesthesia was used. A midline

incision was made above and below the umbilicus. The dissection of Lardennois and Okinczyc was impossible; the detachment of the colic angles was easy. The ileum was cut 5 cm. above the Bauhin's valve with cautery. The incision of the colon was made with the scalpel as near as possible to the rectum, followed by application of 5 per cent tincture of iodine. The distal opening was 8 cm. in diameter. The end of the ileum was closed. Side-to-end anastomosis between the ileum and the sigmoid was made. When the anastomosis was finished the patient died of heart syncope.[5]

CASE 4.—*History.*—J. S., a workman, aged 42, was admitted to the hospital de clinicas, July 15, 1924. He had measles during childhood, and complained of chronic intestinal stasis for twenty years. He had tried several treatments but poor results were obtained. The year before this admission he came to the hospital and a fecaloma was removed.

Present Illness.—He complained of being unable by all means tried to move his bowels, and stated that from time to time he had abdominal pain. When a certain amount of gas was eliminated the pains were not so frequent nor so severe. Purgatives and enemas had entirely failed. At the hospital, after previous anal dilatation, the fecaloma was taken out.

Operation.—A few days afterward when the patient was in better condition and the colon was partially emptied, the operation was performed, Dr. F. Olmedo assisting me. Spinal anesthesia was used (0.1 procaine). The operation lasted one hour and forty-five minutes. A midline laparotomy was done. The sigmoid flexure had attained a gigantic size and the remainder of the colon was larger than normal. The left colic angle was surrounded by strong and old adhesions. The separation of Lardennois and Okinczyc was possible. The total resection of the colon was easy, except for the left angle. The colic arteries were individually ligated. The ileum was cut 5 cm. above the Bauhin's valve, and closure of the proximal end was made by De Martel's method. The sigmoid flexure was cut as far down as possible. The distal opening (10 cm.) was three times wider than the lumen of the ileum. The anastomosis was made following the plan shown in figure 2 (anterior convexity of the ileum), using waxed linen in the three rows of continuous stitches. Intestinal drainage was instituted through the anastomosis by means of a rubber tube.

The patient made an uneventful recovery and left the hospital twenty days afterward perfectly well.

Two months later he came again with a small fecal fistula located in the lower third of the operative scar. He said that ten days before he had noticed a painful spot on the lower abdomen, which gave place afterward to a swollen area. The latter broke down, discharging a certain amount of gas and intestinal contents, after which he had immediate relief.

It seemed probable that the unabsorbable material was the cause of the fistula. Under local anesthesia, avoiding the peritoneal cavity, I enlarged the fistulous tract, removing two pieces of waxed linen which were floating in the intestinal lumen.

The patient left one month later, relieved of the fistula and moving his bowels three times a day.

One year later he was reported to be in good health.

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5. The chloroform was doubtless the main factor.

If the difficulties are considered which one has to overcome in making a total colectomy where there is a megasigmoid flexure, one of them is doubtless the enormous size of the distal opening (sigmoid). To my mind this is the most serious difficulty; even with a folding of it[6] helped by a great elasticity of the ileum, it would be impossible to make an end-to-end anastomosis. Three ways can be followed to obviate the inconvenience: (*a*) an end-to-end anastomosis without folds, similar to the Billroth 1 between the stomach and the duodenum; (*b*) end (ileum) to side (sigmoid) anastomosis, and (*c*) side (ileum) to end (sigmoid) anastomosis.

I have preferred the third variety, which, in my judgment is free from the inconveniences of the other two. The possibility of leakage at the junction of the three suture lines in the first procedure and the making of a side opening through a somewhat altered intestinal wall (rectum and sigmoid) in the second method, seems to be undesirable.

TECHNIC OF THE SIDE-TO-END ANASTOMOSIS

In side-to-end anastomosis the end of the ileum should be closed, preferably using De Martel's procedure. Before approximating both portions it is necessary to carry all the small intestine toward the upper part of the abdomen. The proximal portion is drawn backward until it lies beside the remaining mesentery of the sigmoid flexure. The ileum describes when it is placed correctly "an anterior convexity," as can be seen in figure 2. The side opening (ileum) is made opposite the border of the mesenteric attachment and begins 2 cm. from De Martel's closure and should be as long as the distal opening (sigmoid).

I suggest in regard to the material that should be used for the anastomosis that it is preferable to employ chromic catgut 00 rather than linen to avoid the possibility of an intestinal fistula (case 4).

The first row (outer line) is seroserosa; the second line of continuous suture (middle row) goes through the seromuscular coats and the third row (inner line) stitches both mucous coats along the first half. All the coats are brought together during the second half. After finishing the three concentric suture lines the proximal end is fixed posteriorly.

Finally, the window between the mesentery and the mesocolon should be closed with a continuous suture.

Indispensable Precautions.—There is a natural tendency to perform the anastomosis in the wrong way (fig. 1). I wish to recall that in describing case 1 I stated that on finishing the anastomosis the ileum presented a twist of 180 degrees around its longitudinal axis. The

6. Bosch-Arana: Tecnica de la colectomia, Semana méd., June 14, 1917.

anastomosis was undone and made as is shown in figure 2. When we proceeded in this way no twist was observed.

Causes of the Twist of the Ileum.—If we judge by the observation in case 1 and by dissections in the necropsy room, an important cause of the twist of the ileum is the divergent attachment of the mesentery of the ileum and of the mesosigmoid flexure on the posterior abdominal wall; the former holds and pulls the ileum to the right and the latter to the left or at least fixes the lower portions of the sigmoid flexure in the midline (fig. 3).

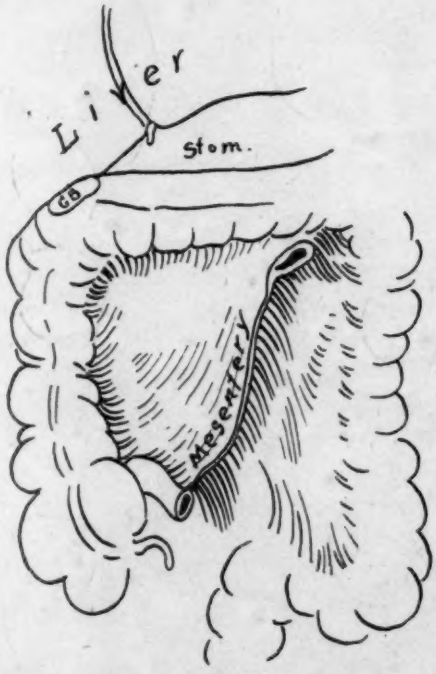

Fig. 3.—Attachment of mesentery, to show pull exerted on ileum in the production of the undesirable twist.

If the operation is carried out following the plan presented in figure 1, it follows that the portion of the ileum in which the side opening is made is twisted clockwise when the last rows of suture line are being made. The attachment of the mesentery (fig. 3) at any rate prevents the adjacent ileum following the clockwise twist, and is likely to produce opposite rotation when the mesentery is very short.[7] In the necropsy room I had no chance to find a body with a megasigmoid flexure; therefore, I was unable to draw any conclusion. But it seems to me evident

7. The Spanish anatomist, P. Aras, who is at present teaching at Cordova Medical School, states that the shortness of the mesentery is perhaps the most important factor.

that with a normal sigmoid flexure a certain degree of adaptation, owing to its soft and thin wall, diminishes the obstructive rotation.

Result of an Intestinal Obstruction Caused by a Twist of 180 Degrees.—A rotation of 180 degrees around the intestinal axis has killed a dog. An unexpected chance provided me an interesting experience when I submitted several dogs to the method suggested by Thorn-

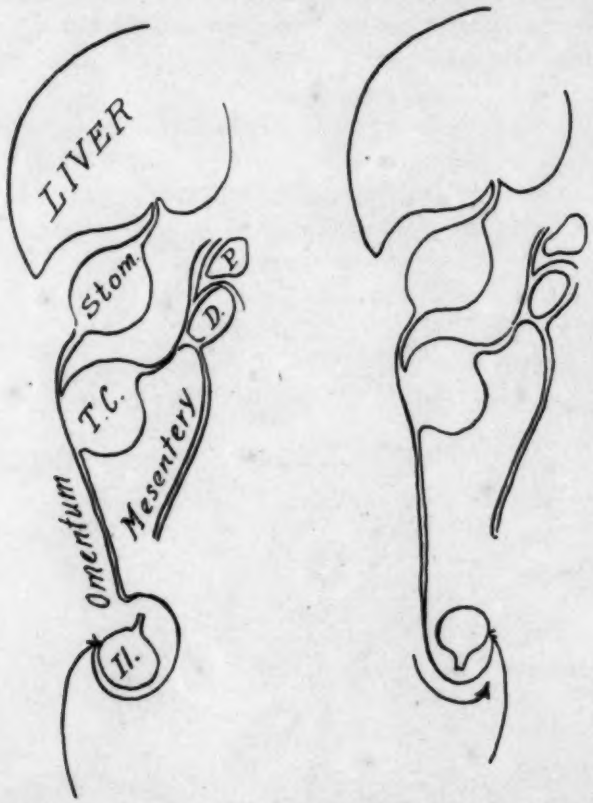

Fig. 4.—Left: portion of ileum detached from mesenteric vessels and wrapped in omentum; right: mechanism of twist of ileum.

burg and Mosckowitz [8] with the purpose of testing its value. The following is the observation:

Dog 2 was operated on, Jan. 29, 1922, at 11 a. m. Ten centimeters of small intestine (ileum) was detached from its mesentery. The intestinal loop became pale and shrunken; the peritoneum lost its brightness. The portion disconnected from the mesenteric vessels was wrapped up with omentum as can be seen on the anteroposterior cross section, figure 4, left.

8. Thornburg and Mosckowitz, quoted by Ochsner: Surgical Diagnosis **3**:27.

January 30 and 31, the dog was vomiting a good deal and appeared exhausted; at four o'clock, January 31, the animal died.

Postmortem Examination.—The peritoneal cavity was free from any fluid. The specimen was carefully removed and it was only found that the detached intestine had twisted 180 degrees around its axis; the rotated loop showed neither adhesions with the omentum nor necrotic points. The afferent intestine of size twice larger than normal had a cyanotic aspect and was free from either fluid contents or necrotic spots. The efferent portion had a normal aspect and was empty.

The dog died of an intestinal obstruction. The 180 degrees twist was caused by the weight of the omentum and the normal standing position of the dog (fig. 4, right). This observation shows the fatal result of such intestinal obstruction.

GIANT CELL TUMOR OF BONE*

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Of the various types of bone neoplasms none, perhaps, have been or are the subject of more interest and discussion among surgeons and pathologists than the so-called giant cell tumors, often referred to as giant cell sarcoma of the epulis type, myeloid sarcoma or osteoclastoma. We have known of this bone lesion for more than eighty years from the work of Lebert[1] and, although much study by many capable men has resulted in a general familiarity with its clinical, roentgenologic, pathologic and histologic characteristics, our knowledge of the true nature, behavior and course of the tumors of the giant cell series remains far from complete, and our interpretation of their structure is quite unsatisfactory. Some students, notably Barrie[2] and his followers, have regarded the tumor as being a local, chronic, inflammatory process; others feel that it is a true neoplasm. We are not certain of the origin or significance of the giant cells that are characteristically present. Bone, marrow, foreign body and endothelial origin have been ascribed to them by different investigators; some consider them as osteoclasts, actively functioning as absorbers of bone, while a few hold they are incidental to, and not an integral part of, the tumor. Histologically, some pathologists consider them, particularly their number and their type of nuclei, as indexes to the relative malignancy of the growth; others rely on the cellularity and cell morphology of the stroma as being the criteria of the tumor's aggressiveness. Ewing,[3] in describing the giant cell tumor and its variants, emphasizes that a study of the stroma offers a standard for differentiating between giant cell tumor and medullary osteogenic sarcoma, secondarily containing giant cells, and is inclined to restrict the importance of the giant cells themselves. There is at present a tendency to regard the giant cell tumor as essentially benign, yet numerous cases have been reported that have terminated fatally. These, on careful study, often have been shown to be true sarcomas, secondarily containing giant cells, and naturally have been confusing. In addition to these, however, an occasional atypical case is met with, which,

* From the Laboratory of Morbid Anatomy, Philadelphia General Hospital.

1. Lebert, H.: Des tumeurs fibro-plastiques ou sarcomateuses, Physiologie pathologique, Paris, J. B. Bailliere et fils **2**:120, 1845.

2. Barrie, G.: Chronic (Nonsuppurative) Hemorrhagic Osteomyelitis, Ann. Surg. **57**:244 (Feb.) 1913; **71**:581 (May) 1920.

3. Ewing, J.: A Review and Classification of Bone Sarcoma, Arch. Surg. **4**:494 (May) 1922.

although locally malignant and in a few instances actually metastasizing, apparently does belong to the giant cell tumor group.

The history of the giant cell tumor is interesting in that practically all contributions on the subject include references to giant cell tumors that have been atypical and malignant. Paget [4] in 1854, describing and referring to the condition as myeloid tumor, called attention to the general innocent nature of the tumor, but recognized that an occasional growth, apparently similar, often ran a malignant course. Nélaton,[5] a few years later, classically described the characteristics of the tumor both clinically and histologically, but noted that aytpical cases, which presented an increase in the proportion of spindle cells that became malignant. Gross [6] in 1879 differentiated between, on the one hand, the typical giant cell tumor, a spherical growth enclosed in an osteomembranous capsule, usually occurring in the spongy substance of the epiphysis, red to maroon and of spongy and jelly-like consistency, resembling exuberant, vascular granulation tissue and containing no vestige of the original bone, and, on the other hand, a confusing malignant tumor, generally similar but lighter in color and with multiple foci of calcification and ossification throughout its substance.

More recently Bloodgood's [7] contributions have been largely responsible for the present day attitude of the benign nature of the giant cell tumor held by many surgeons and pathologists. In a study of 177 cases over a period of thirty-two years, he has not observed metastasis, despite recurrence in some twenty-four instances, and 100 of these were well three to thirty years after operation. Codman [8] regards giant cell tumor as a benign mass of granulation tissue and affirms Bloodgood's findings; Martland [9] also emphasizes the benign nature of the lesion, and believes that it is an inflammatory process and a phase of osteitis fibrosa cystica. Meyerding [10] studied twenty-four cases of giant cell tumor, fifteen of

4. Paget, James: Lectures on Surgical Pathology, Philadelphia, Lindsay and Blakiston, 1854, lecture 28, part 1, p. 446.

5. Nélaton, E.: D'une nouvelle espèce de tumeurs benignes des os, ou tumeurs à myéloplaxes, Paris, 1860.

6. Gross, S. W.: Sarcoma of Long Bones, Am. J. M. Sc. **78**:17, 1879.

7. Bloodgood, J. C.: Bone Tumors, Ann. Surg. **69**:345 (April) 1919; Benign Giant Cell Tumor of Bone, Its Diagnosis and Conservative Treatment, Am. J. Surg. **37**:105 (May) 1923; The Giant Cell Tumor of Bone and the Specter of the Metastasizing Giant Cell Tumor, Surg. Gynec. Obst. **38**:784 (June) 1924.

8. Codman, E. A.: The Nomenclature Used by the Registry of Bone Sarcoma, Am. J. Roentgenol. **13**:105 (Feb.) 1925.

9. Martland, H. S.: Primary Bone Tumors: Their Classification with Special Reference to Benign Giant Cell Tumor, Proc. New York Path. Soc. **21**: 102, 1921.

10. Meyerding, H. W.: Benign Foreign Body Giant Cell Tumors in the Long Bones, J. A. M. A. **83**:1323 (Oct.) 1924.

which were treated by primary curettage, five by amputation, three by resection and one by excision, and, although five of these were in turn treated by secondary amputation following recurrence and infection, he found no instance of true malignancy and concluded that they were benign lesions of inflammatory origin containing foreign body giant cells.

On the other hand, many present day students do not consider giant cell tumors altogether benign. Stewart,[11] in an analysis of fifty cases, found no evidence of dissemination, but because of the likelihood of recurrence regarded the tumor as a true neoplasm and as locally malignant. Stone and Ewing,[12] in a critical review of the literature, were able to find no proved instance of a giant cell tumor having metastasized but reported a case of giant cell tumor of the tibia which, following repeated currettage, infection and irradiation, changed into a large spindle cell sarcoma without giant cells and caused death from pulmonary metastasis. MacGuire and McWhorter,[13] in a study of twenty cases, found that following treatment there was no recurrence in twelve instances, but that of the remaining eight cases, seven recurred locally, two of which metastasized to the lungs, one to the inguinal glands and abdomen, and one massively involved an amputation stump. Coley's [14] review of fifty cases showed that thirty-two of the patients were well without signs of recurrence as an end-result of treatment, and that ten had died from metastasis, and, in considering the various cases of alleged malignancy reported in the literature, concluded that it was difficult to explain matters on the assumption of mistaken diagnoses in all instances. Kolodny [15] cites four cases, one of which gave pulmonary metastases without giant cells, and intimates that the pendulum is swinging backward, reaffirming views formerly held regarding the relative malignancy of giant cell tumor.

The following cases, recently studied, illustrate the features of the typical giant cell tumor, essentially benign at one end of the series and relatively locally malignant at the other, but possessing anywhere along the scale the inherent power of becoming essentially a malignant tumor which, under proper stimuli, may rarely assert itself. A true sarcoma,

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11. Stewart, M. J.: Observations on Myeloid Sarcoma with an Analysis of Fifty Cases, Lancet **2**:1236 (Nov.) 1914.

12. Stone, W. S., and Ewing, J.: An Unusual Alteration in the Natural History of a Giant Cell Tumor of Bone, Arch. Surg. **7**:280 (Sept.) 1923.

13. MacGuire, C. J., and McWhorter, J. E.: Sarcoma of Bone; An Analysis of Fifty Cases, Arch. Surg. **9**:560-584 (Nov.) 1924.

14. Coley, W. B.: Prognosis in Giant Cell Sarcoma of Long Bones, Ann. Surg. **79**:321 (March) 1924.

15. Kolodny, A.: Diagnosis and Prognosis of Bone Sarcoma, J. Bone & Joint Surg. **7**:936 (Oct.) 1925.

secondarily containing giant cells of the epulis type, is cited as an example of the central bone tumor which, we feel, is often incorrectly diagnosed as benign giant cell tumor, and is largely responsible for the confusion that exists. I am indebted to the surgeons mentioned for the clinical data used in this study.

REPORT OF CASES

CASE 1.—*History.*—W. H., a white patrolman, aged 31, entered the Philadelphia General Hospital, Feb. 28, 1922, in the service of Dr. Hubley B. Owen, with the

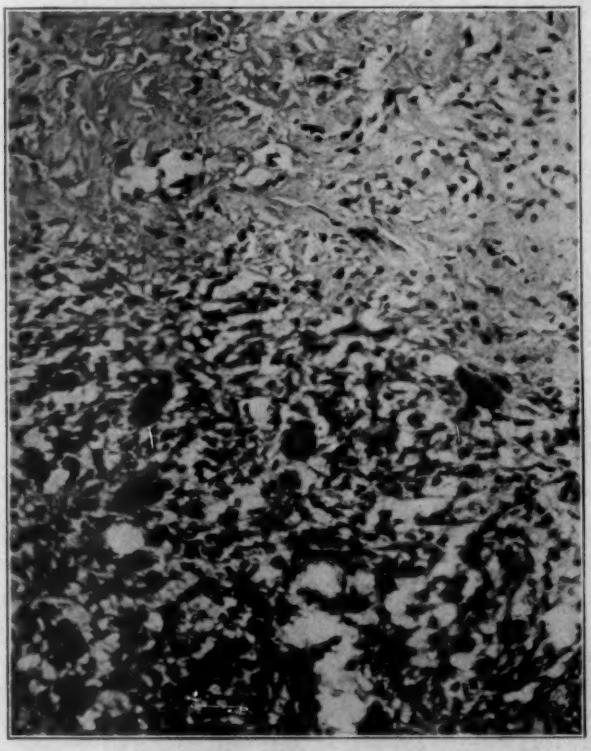

Fig. 1 (case 1).—Structure of a benign giant cell tumor well down the scale; dense adult fibrous tissue stroma, relatively acellular above but composed of mature fibroblasts and infiltrated with lymphoid cells below; several multinucleated osteoclasts, or giant cells of the epulis type, are seen in the more cellular areas; ×275.

history that one year previously he had fallen, striking the right leg below the knee. For four days he was unable to walk. He recovered and returned to work but noticed sharp pains in the region of the injury "off and on." Four months ago, and again two months ago, he fell, each time injuring the right knee. He noticed slight enlargement of the knee after the second fall, and at times it was red and hot. For the last four months he had been unable to work and on admission walked with the aid of a crutch.

On physical examination there was slight swelling immediately below the right knee, apparently involving the head of the tibia. This swelling was irregular in outline, not tender to pressure, and was neither red nor hot. The other physical findings were of no consequence. The laboratory examinations were negative, and a roentgenogram taken March 1 showed "bone expanded in the head of the tibia; cortex thinned, but intact; bone rarefied, with trabeculae running through this area, giving it a multilocular, cystic appearance."

A diagnosis of giant cell sarcoma was made and, March 7, the tumor was removed by Dr. Owen by curettement to healthy bone. Convalescence was uneventful. The incision healed well. A cast was applied; the patient used crutches for six months and when seen in April, 1926, was on active patrol duty with no complaint of any kind.

Pathologic Examination.—The gross specimen consisted of many small irregular pieces of friable tissues, each having a layer of white, lusterless, dense tissue, to which were attached soft, spongy, dark reddish granulations, all intermingled with blood clot. Microscopically, the stroma was an ill-defined, loose, fibrous meshwork, moderately well infiltrated with small, rounded lymphoid and larger polygon shaped mononuclear cells in places, and was of fairly dense, wavy, hyalofibrous character, practically acellular, in others (fig. 1). Here and there small patches of large giant cells with abundant, opaque, acidophil cytoplasm, and containing numerous, small, oval nuclei centrally placed were noted. Spindle cells or active cells of any kind were not demonstrated; the striking feature, histologically, was the relatively acellular adult fibrous stroma, which suggested that the growth was of extremely benign nature.

Case 2.—*History.*—E. G., a white married woman, aged 23, came to the Radiological Clinic of the Philadelphia General Hospital, April 21, 1926, with the history that three months previously she had turned her right ankle while walking. One month later she first noticed pain in the right knee, laterally. This pain was dull in character and was especially marked on walking or when the knee was pressed on. Swelling was never noticed. The condition became progressively worse, and during the two weeks prior to admission the knee often gave way when she was walking. No history of injury was elicited. Because of a congenital dislocation of the right hip, she had always limped; this had not increased because of the knee condition.

On physical examination there was definite fulness of the lower lateral half of the right knee, and on palpation there was tenderness immediately over the epiphysis of the fibula. The knee was stiff on passive motion, but function was not greatly disturbed. The right leg was 2 inches (5 cm.) shorter than the left because of the hip dislocation. The other physical findings were unimportant, and the routine laboratory examinations were negative.

Roentgen-ray examination revealed an expanded, rarefied, well circumscribed area involving all the head of the fibula, a picture typical of giant cell tumor (fig. 2).

April 22, Dr. J. B. Carnett resected the upper 3 inches (7.6 cm.) of the fibula, removing the growth intact. Convalescence was uneventful. The incision healed by first intention, and the patient was discharged from the hospital, May 10, in excellent general condition.

Pathologic Examination.—The head of the fibula was replaced by a solid, easily pliable tumor, ovoid in shape, and measuring 4.5 by 3.5 by 3 cm. The wall limiting the growth was everywhere intact, and was continuous with the periosteum of the fibula. It contained several small, flat, bony plaques.

On section (fig. 3) the tumor was seen as a ballooned-out, thin walled, osteomembranous sac filled with dark purplish red to maroon colored, cellular, friable tissue grossly resembling hyperplastic bone marrow. Of uniform consistency throughout, this tissue tended to separate either into firm, jelly-like chunks, or adhere to the tumor wall. No cysts or areas of degeneration were present.

Fig. 2 (case 2).—Right knee showing a neoplasm occupying the head of the fibula; the expanded, rarefied, well circumscribed area involving all the epiphysis of the fibula forms a picture characteristic of giant cell tumor.

The marrow cavity of the fibula extended up to the tumor where tumor substance and marrow merged into each other.

Histologic Examination.—Great numbers of giant cells of the epulis type or osteoclasts, varying much in size, and containing varying amounts of finely granular, acidophil cytoplasm, often vacuolated, and from ten to sixty small, ovoid, centrally placed nuclei with prominent nucleoli were seen more or less uniformly

embedded in a stroma composed of loose intercellular, fibrous reticulum (figs. 4 and 5). A few elongated, adult fibroblasts were seen here and there. Numerous rounded and polygon shaped cells, each containing a large vesicular nucleus and a considerable amount of rather deeply staining cytoplasm were scattered through the stroma. These had the general morphology and appearance of osteoblasts or liberated bone cells. At the periphery small plaques of bone surrounded by osteoblasts and a dense layer of fibrous tissue were seen. The stroma showed no evidence of unusual growth, and the general picture was characteristic of benign giant cell tumor.

Case 3.—*History.*—N. P., an Irish girl, aged 25, entered the Radiological Clinic of the Philadelphia General Hospital, Aug. 12, 1925, complaining of pain and swelling in the right knee and inability to walk without crutches. In February, 1924, eighteen months previously, she had first noticed pain in the knee when

Fig. 3 (case 2).—Giant cell tumor of the head of the fibula treated by resection; ballooned-out osteoperiosteal sac filled with chunks of friable, cellular, bone free tumor substance; the limiting tumor wall is everywhere intact; a bony shell is seen circumscribing the growth in places.

standing, usually more pronounced in the morning. There was no history of injury. This condition had slowly grown worse and the knee had become somewhat swollen. For the four months preceding admission she had been unable to walk without crutches. It is interesting that because of a vaginal discharge, which proved to be of nonsyphilitic nature, the condition was thought to be a gonorrheal arthritis in three different hospitals, and was treated by baking, a roentgen-ray examination never having been made.

Physical examination revealed a swollen, stiff knee and slight pitting edema of the right leg and foot. The knee was slightly tender to pressure. The other physical findings were unimportant. The routine laboratory examinations were negative and the Wassermann reaction was negative. Roentgenologic study (fig. 6) showed a circumscribed rarefaction, diffusely mottled, occupying the greater

part of the epiphysis of the right femur, and practically all of the external condyle. A narrow bony rim bordered the scallops of this area on the internal side, but was lost on the extreme fibular side. Except for this irregularity, the area of bone tissue loss presented a multiple, coalescing, cystic appearance.

September 12, the leg was amputated at the level of the middle and lower third of the thigh. The wound healed by first intention, convalescence was

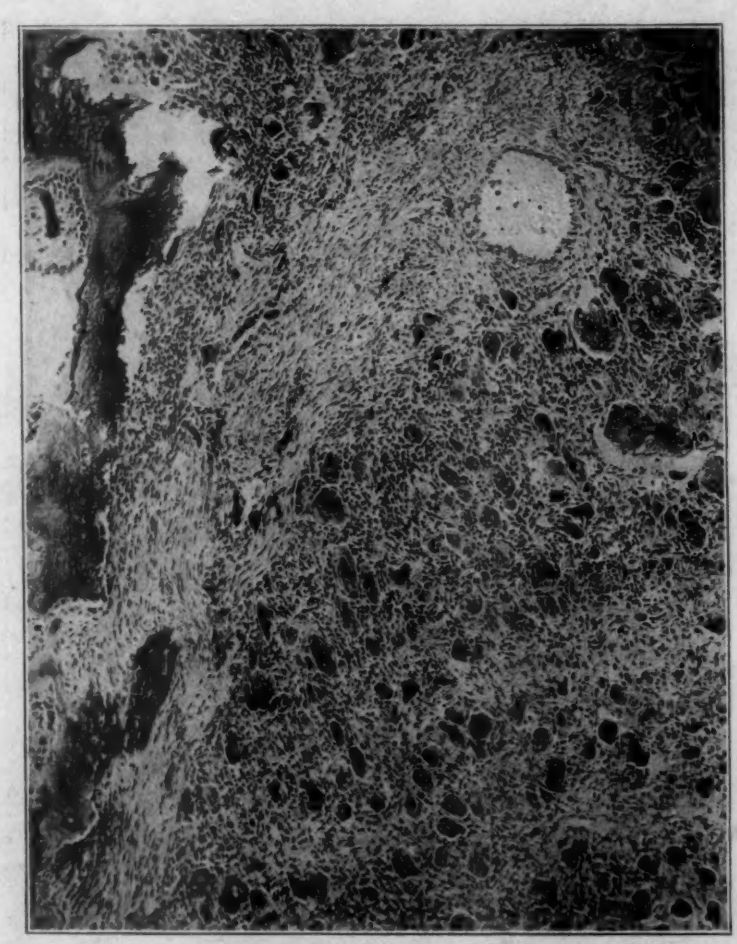

Fig. 4 (case 2).—Structure of a typical giant cell tumor: Limiting periosteal wall containing small plaques of bone should be noted. Many osteoclasts, or giant cells of the epulis type, and containing from fifteen to forty small, ovoid, deeply staining, centrally packed nuclei are scattered diffusely throughout the stroma; ×90.

uneventful, and when seen in April, 1926, the patient was in excellent health and without recurrence.

Pathologic Examination.—Grossly, when the soft tissues were dissected away from the femur, an irregular enlargement of the epiphysis, especially laterally, was noted. On the fibular side, a rather dense but relatively soft mass was

palpable through the periosteum. Nowhere had the tumor perforated or broken through the periosteum. On section (fig. 7) a well differentiated mass, roughly the size of an orange, and surrounded by a narrow rim of bone everywhere except on the fibular side, occupied all of the external condyle and a large part of the epiphysis. Its center was golden yellow and cheeselike and appeared necrotic; an irregular peripheral zone, averaging from 1 to 2 cm. in thickness, was of mottled

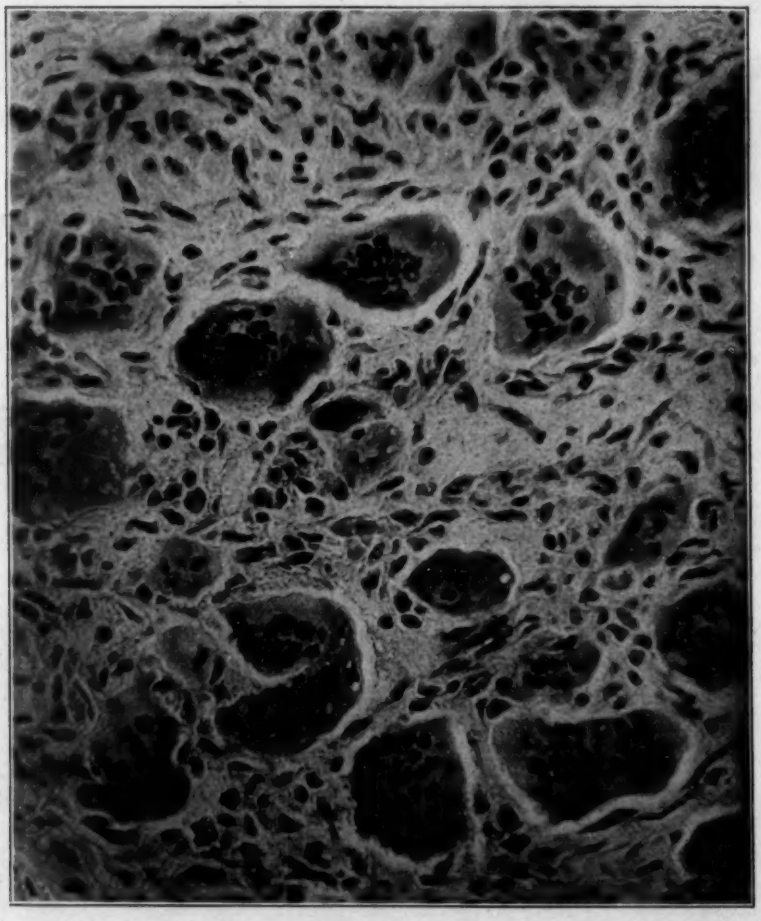

Fig. 5 (case 2).—Stroma composed of fine fibrous reticulum and numerous mature, elongated fibroblasts, under high power; in addition to the osteoclasts, many modified osteoblasts that have failed to eventuate into giant cells are seen embedded in the stroma.

gray red to deep wine color, and showed numerous small, rounded, firm, deep red, jelly-like patches. The tumor tissue was soft, friable and relatively bloodless, and no bony spicules were encountered.

Histologic Examination.—At the extreme periphery many small islands of bone tissue were seen (figs. 8 and 9). These were closely surrounded by a layer of cells, each containing one rounded, deeply staining nucleus, and a considerable

amount of granular, opaque cytoplasm. These had the general morphology of osteoblasts. Numerous large multinucleated giant cells of the epulis type were seen nearby, usually on the inner side of the bone plaques. These were interpreted as osteoclasts which were absorbing bone nearly as fast as it was formed. Many of these osteoclasts and numerous polygon shaped, mononuclear cells resembling osteoblasts or liberated bone cells were embedded diffusely throughout the tumor in a groundwork composed chiefly of loose fibrous reticulum and elongated, mature fibroblastic cells, which presented no signs of activity. A few

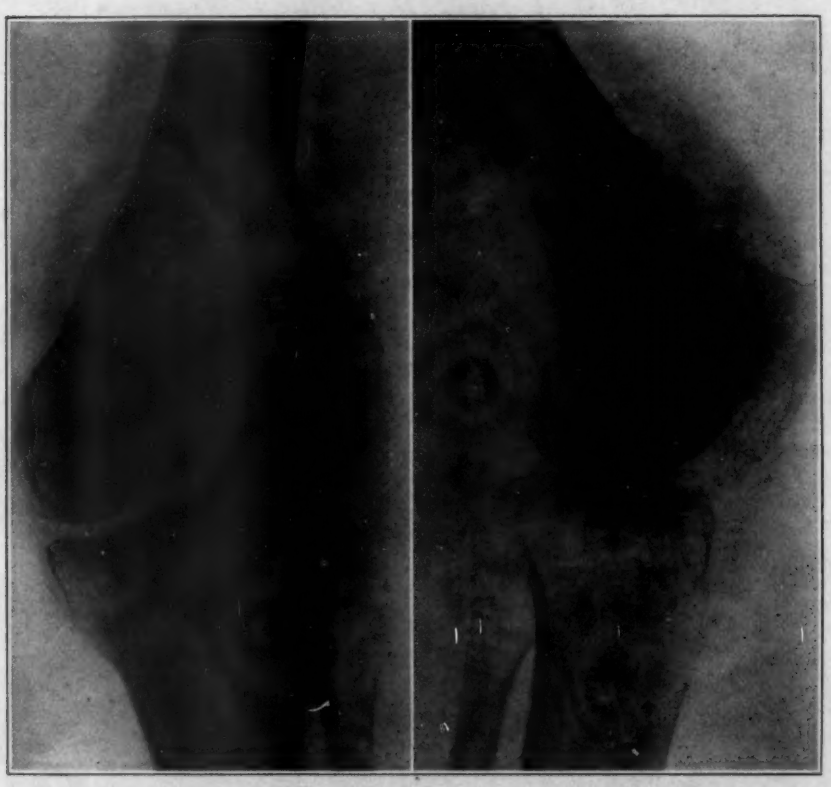

Fig. 6 (case 3).—Right knee, anteroposterior and lateral views, showing a neoplasm growing in the epiphysis of the femur; the rounded, mottled area of diminished density, bordered by a narrow, bony rim in places and with a scalloped periphery generally, forms a picture suggestive of multiple coalescing cysts but characteristic of giant cell tumor; only the periosteum limits the growth on the extreme fibular side.

poorly formed capillaries were noted. Sections from the central portion of the tumor showed that much of the growth had degenerated and had become necrotic. Microscopically this neoplasm presented no evidences of true malignancy, and was considered a benign giant cell tumor.

CASE 4.—*History.*—G. H., a white man, aged 32, entered the Polyclinic Hospital, March 11, 1923, in Dr. J. B. Carnett's service, complaining of pain in the right leg below the hip. Six months before he first noticed that when weight

was borne on the right leg there would be pain deep in the thigh, about 4 inches (10.1 cm.) below the hip. There was no history of injury. The condition had become only slightly worse, and two weeks before admission he had received an application of radium, which had practically relieved his pain. Physical examination was essentially negative, except for slight swelling of the greater trochanteric region on the right side. Motion of the thigh was not affected and there was no tenderness. The laboratory findings were negative. Roentgen-ray examination revealed rarefaction of the neck and trochanter of the femur, surrounded by a

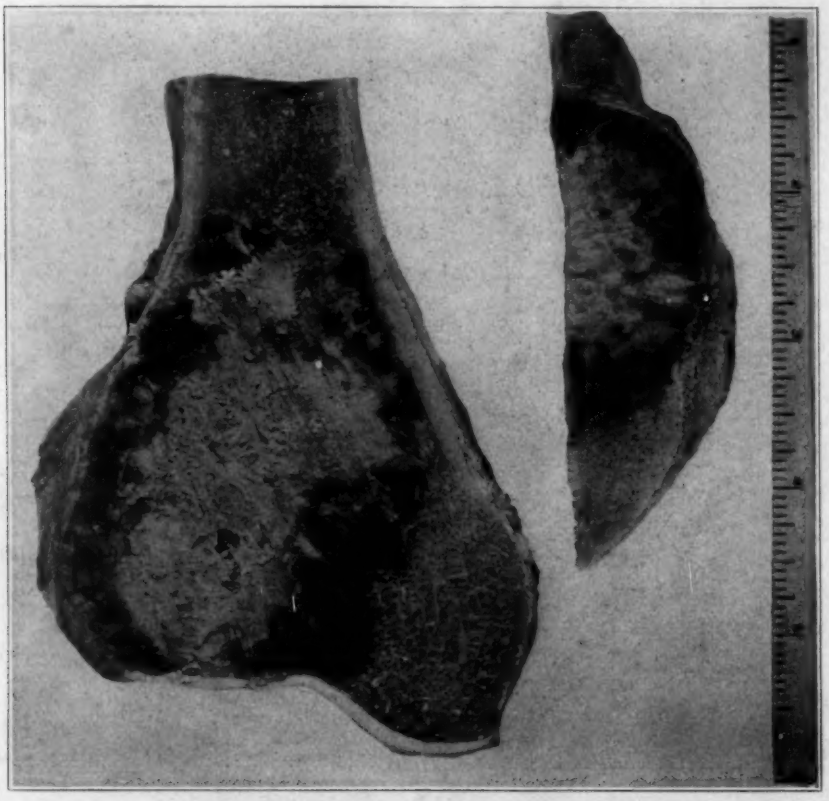

Fig. 7 (case 3).—Femur showing a solid giant cell tumor occupying the greater part of the epiphysis; the irregular, dark patches at the periphery of the growth were maroon, jelly-like pockets in the fresh specimen; the center was yellowish and cheeselike; growth has not perforated the periosteum anywhere; the bony rim surrounding the tumor can be seen in places.

narrow rim of bone, everywhere intact (fig. 10). The contiguous bone appeared normal. The circumscribed area measured approximately 3 by 4 by 5 cm. A diagnosis of central sarcoma was made and, on March 23, the tumor was removed by Dr. Carnett by thorough curettement. Convalescence was uneventful. Roentgenograms made in November, 1923, eight months after operation, showed that recalcification to the extent of normal density had occurred. In April, 1926, the patient was well without signs of recurrence and was actively engaged in business as a traveling salesman.

Pathologic Examination.—The gross specimen consisted of several small chunks of reddish, firm, friable tissue, intermingled with considerable blood clot. No bone elements were demonstrable. Microscopic study of sections taken from different portions of the growth all gave the same picture (fig. 11). Large cellular patches composed of fine, loose, fibrous reticulum in which mature appearing fibroblasts grew in all directions formed a dense ground substance, throughout which many giant cells of the epulis type, or osteoclasts, were scattered. Imperfect capillaries were noted here and there and in places areas of hemorrhage were

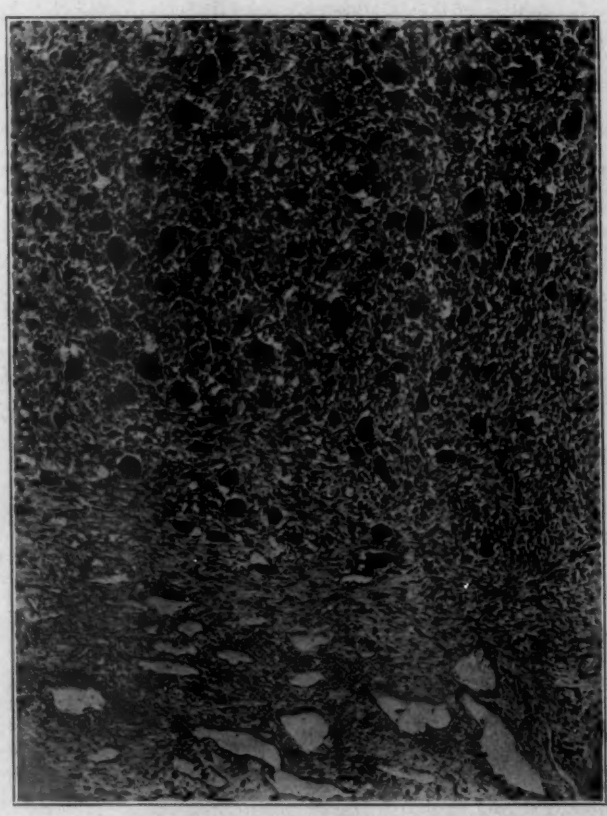

Fig. 8 (case 3).—More cellular giant cell tumor; many osteoclasts are scattered through the growth; the numerous osteoblasts, or liberated bone cells that have not taken part in giant cell formation, give the stroma an increased but pseudocellularity; × 115.

prominent. This neoplasm, although possessing an unusually cellular stroma, showed no evidences of cell activity or malignancy, and because of the general adult appearance of its stroma, was regarded as a benign giant cell tumor.

These four cases are rather typical examples of the benign giant cell tumor, the most common of the central bone lesions. Occurring characteristically in the epiphyses of the long bones of young adults, with pain and swelling as initial symptoms, the disease progresses slowly and

in from three to eighteen months disturbance of function becomes the chief complaint. The roentgenograms in each instance show typically the circumscribed, diffusely mottled, rarefied area produced by the bone absorption activity of the everexpanding growth. Histologically, all four cases are benign. Osteoclasts, or giant cells of the epulis or foreign body type, are present in each in varying numbers and their significance, aside from the fact that they characterize the tumor by their presence, appears to be that of functioning mainly as bone absorbers. The stroma

Fig. 9 (case 3).—Same section as shown in figure 8 under high power, showing the loose stroma, composed of a fine, fibrous reticulum and numerous adult elongated fibroblasts, which show no signs of activity; the polygon shaped mononuclear cells embedded in the stroma have the general morphology of osteoblasts and represent the liberated bone cells that have failed to fuse into polynucleated osteoclasts.

ranges from a relatively acellular fibrous matrix in case 1 to increasingly cellular structures composed chiefly of fibrous reticulum and fibroblastic cells in the other three cases, but in no instance do these cells show unusual behavior or activity. In each case the general adult appearance of the stroma is a fair criterion of the innocence of the tumor, and the follow-up shows that all four patients are well without signs of recur-

rence, four years, one month, seven months and three years after operation, respectively.

CASE 5.—(Drs. M. B. Cooperman and E. A. Case, Polyclinic Hospital).—*History.*—L. G., a white man, aged 34, stated that in 1916 he struck his left knee against a chair. Pain and slight swelling followed. Dry heat and hot baths were employed, but the condition failed to improve and in a few months he entered the Polyclinic Hospital, where a diagnosis of giant cell tumor was made. Thorough curettement of the tumor was done in 1917, one year after the initial injury.

Fig. 10 (case 4).—Pelvis showing a neoplasm occupying the neck and trochanter of the right femur; a narrow rim of bone surrounds the mottled area of diminished density and forms a picture typical of giant cell tumor. The growth was removed by thorough curettement and there has been no recurrence in three years.

The growth recurred after a period of apparent cure, and in 1919 a second curettement was done. Little benefit resulted from this; a second recurrence was soon evident, and on the third admission to the hospital the patient complained of inability to use the left leg and frequent attacks of sharp, needle-like pains throughout the knee. He had used braces and crutches the last ten months. Physical examination revealed an irregularly enlarged knee, twice normal in size, with complete loss of function. It was tense and tender and quite hard, but softer in spots than in others. Other physical findings were of no consequence,

and the routine laboratory examinations were negative. The Wassermann reaction was negative. A roentgenogram (fig. 12) showed a bone destroying neoplasm involving the upper part and head of the left tibia, the head of the fibula, and the posterior portion of the internal condyle of the femur. The leg was amputated well above the knee in October, 1921.

In August, 1922, the patient again returned to the hospital, complaining of cough, substernal pain on coughing, and of blood spitting of five months' duration. He had lost much weight and had grown progressively weaker. Roentgen-ray exam-

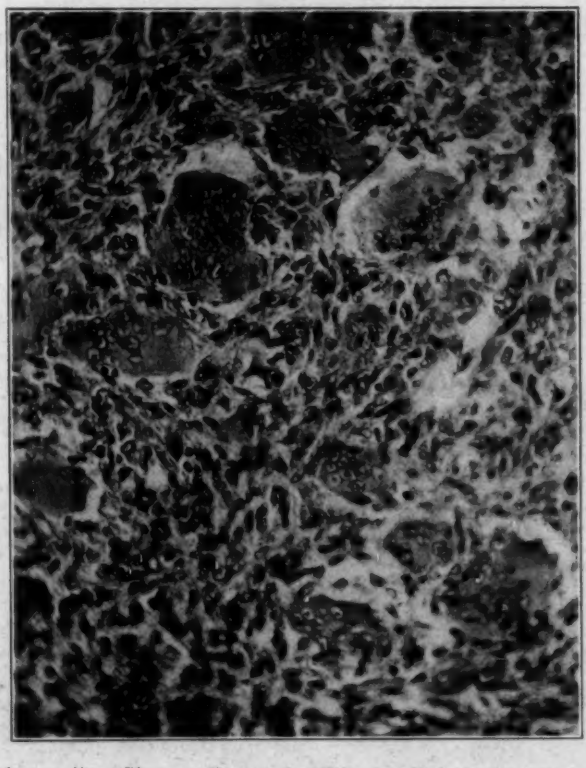

Fig. 11 (case 4).—Giant cell tumor with a cellular stroma; many mature, elongated fibroblasts growing in every direction form this stroma; no mitoses are seen; the osteoclasts are present in large numbers and are uniformly embedded throughout the growth; × 275.

ination of the chest (fig. 13) revealed metastatic lesions in the lungs. The patient failed rapidly and died in November, 1922. Necropsy was not performed.

Pathologic Examination.—Tissues from the first and second curettements unfortunately were not available for this study, but were reported as showing the structure of typical giant cell tumor. Dissection of the tumor in the amputated leg (fig. 14) revealed a destructive, soft, cellular, invasive, sarcomatous growth involving all the bones and soft tissue about the knee joint.

Sections taken from different portions of the neoplasm (figs. 15, 16 and 17) showed many areas composed of closely packed, thick, spindle shaped cells, scattered through which were numerous large, multinucleated giant cells of the epulis

type. Very little fibrous supporting tissue was present. Other areas consisted almost exclusively of spindle cells, relatively constant in size and staining reaction but showing numerous karyokinetic figures, suggesting rapid growth. Still other areas consisted of closely packed, varying sized, deeply staining, rounded or polyhedral cells, scattered through which were many irregular giant cells, not of the

Fig. 12 (case 5).—Left knee region showing the second recurrent neoplasm of the head of the tibia five years after the initial growth and following two curettements; there is massive involvement of the entire knee with destruction of the head of the tibia, fibula and lower part of the femur and obliteration of the knee joint. This neoplasm is basically a giant cell tumor but has undergone malignant transformation.

epulis type, containing varying amounts of cytoplasm and from one to four or five large, deeply staining oval nuclei, many of which were dividing. No areas of calcification or ossification were demonstrable. Dr. E. A. Case of the Polyclinic

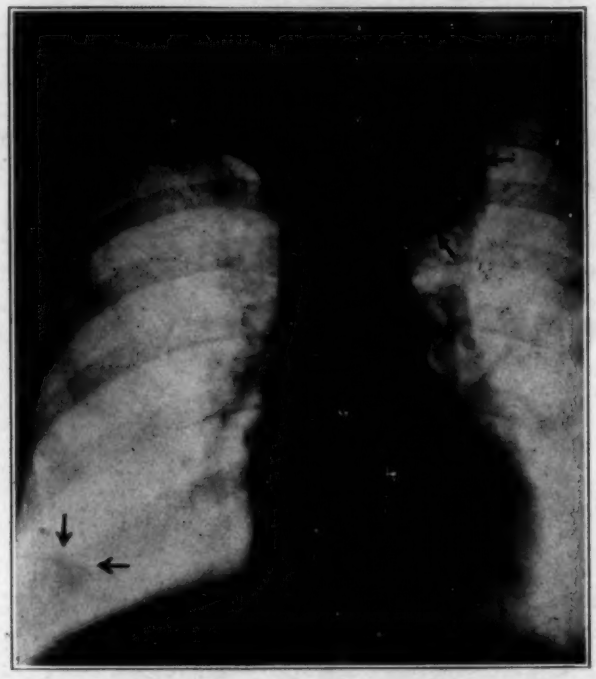

Fig. 13 (case 5).—Chest showing metastatic tumor shadows in the right lower lobe, in the left upper lobe and substernally.

Fig. 14 (case 5).—Massive recurrent giant cell tumor that has become malignant, showing extensive invasion and destruction of soft and bony parts about the knee.

Hospital described the condition as "giant cell sarcoma with a number of areas of actively growing cells," and our study of the various sections suggested that basically the tumor was a true giant cell tumor, which now showed malignant transformation, an opinion in which Dr. James Ewing concurred.

This case is both atypical and unusual. The history, symptoms, behavior and clinical study of the tumor in its early course all point rather strongly to its "benign giant cell tumor" nature originally and, although the tissues and slides from the first and second curettements unfortunately were not available for our study, histologic confirmation may perhaps be assumed on the grounds that the pathologic diagnosis at

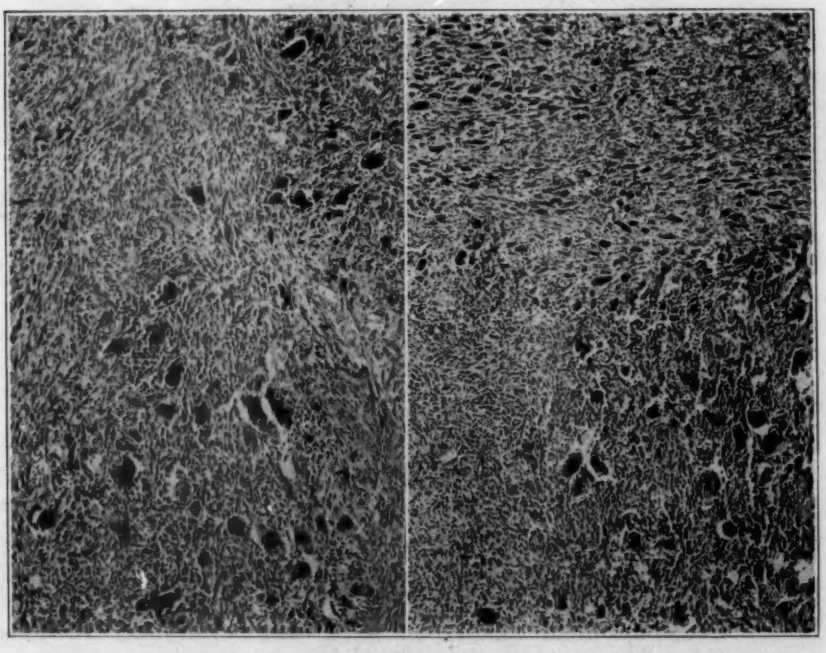

Fig. 15 (case 5).—Structure of a giant cell tumor that has undergone malignant transformation, under low power; the stroma is extremely cellular, composed chiefly of spindle cells and is without giant cells in places; the large giant cells are of the epulis type and were present throughout the growth in patches; the smaller, deeply staining giant cells are of the malignant type.

the time of each operation was "giant cell sarcoma." Microscopic study of tissues obtained at the time of amputation confirms definitely the malignant nature of the growth at this time, yet but for the numerous areas of actively growing, atypical cells, the picture remains basically that of giant cell tumor with a cellular stroma composed chiefly of active, fat spindle cells. The tumor followed injury; was treated by curettement after a year; recurred and was treated again by curettement two years later; recurred a second time with the aspects of malignancy and was

treated by amputation five years after and caused death by metastasis, proved roentgenologically, six and one-half years after the appearance of the original growth; so it would seem that we are dealing with a true giant cell tumor that had undergone malignant transformation. A parallel to this case is one reported by E. F. Finch and H. H. Gleave,[16] microscopic sections from which we have had the privilege of studying, and the salient features of which are as follows:

A man, aged 49, entered the Sheffield Royal Infirmary in December, 1917, with a pathologic fracture of the lower end of the femur, which apparently healed satisfactorily without surgical treatment, and a history of pain in the knee since 1915. A roentgenogram made at this time revealed the presence of a tumor

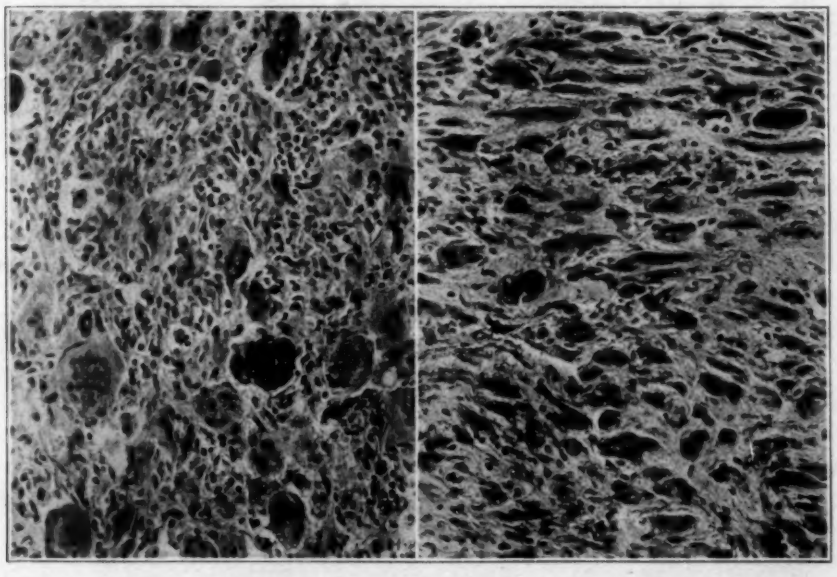

Fig. 16 (case 5).—Recurrent malignant giant cell tumor showing in detail to the left an area fairly typical of giant cell tumor, under high power; the stroma is very cellular and is composed of spindle cells, some of which show mitotic figures; the giant cells are of the epulis type and show no changes; to the right is an area composed of large, plump, spindle cells and giant cells of the malignant type containing large, hyperchromatic nuclei.

at the site of the fracture, and in June, 1920, when there was pain and swelling at the same site, roentgen-ray examination gave a typical picture of central giant cell tumor. The patient refused operative treatment and, fitted with a splint, continued at work as a carpenter until September, 1924, when the pain became quite severe. The leg was amputated in January, 1925, and gross study and dissection showed a typical appearing currant jelly tumor, which had extended

16. Finch, E. F., and Gleave, H. H.: A Case of Osteoclastoma (Myeloid Sarcoma, Benign Giant Cell Tumor) with Pulmonary Metastasis, J. Path. & Bact., to be published.

through the line of fracture into the thigh muscles and which had partially obliterated, but not invaded, the knee joint. Sections from this growth gave a typical giant cell tumor picture with a groundwork of pleomorphic and fibroblastic cells, which contained many osteoclasts, or multinucleated giant cells of the epulis type. In October, 1925, there was a recurrence of the growth in the stump, and a history of hemoptysis of three months' duration. Roentgen-ray examination revealed pulmonary metastasis. The patient died in January, 1926. At necropsy a massive, locally malignant, recurrent tumor, 8 inches (20.3 cm.) in diameter, and involving the whole of the stump, and numerous soft, whitish and hemorrhagic secondary tumor nodules in the lungs were demonstrated. Microscopic study of sections from the stump recurrence gave essentially the same picture as was noted at the time of amputation, except that the stroma was more cellular and showed many mitotic figures. The osteoclasts showed no changes. Sections from the lung

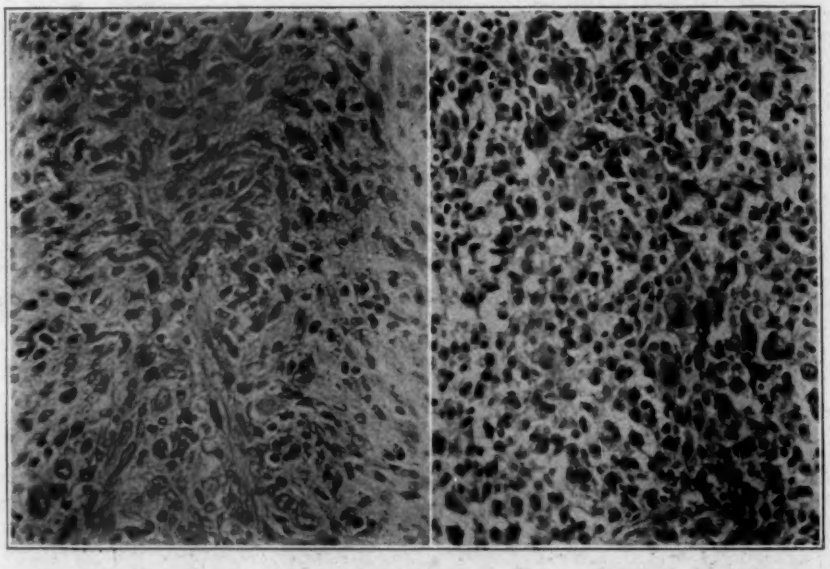

Fig. 17 (case 5).—Same neoplasm as shown in figure 16, under high power, showing to the left a patch of large, rapidly growing, closely packed spindle cells; no giant cells are seen; to the right is an area composed of pleomorphic cells, many showing cell division stages; the picture resembles that of mixed cell sarcoma.

metastases were practically identical with these. The stroma was composed of fibroblastic, actively growing cells, and scattered uniformly throughout many multinucleated osteoclasts were demonstrable.

Case 6 (Drs. E. B. Hodge and J. Eiman, Presbyterian Hospital).—*History.*—S. C., a white man, aged about 22, entered the Presbyterian Hospital in January, 1923, complaining of pain, swelling and tenderness in the left knee. Two months prior to admission he had first noticed soreness and stiffness in the knee joint. There was no history of injury. The condition had grown steadily worse and on admission the joint was practically functionless. Physical examination revealed fluid in the knee joint and fulness about the lower end of the femur. Roentgenologic study (fig. 18) revealed an indefinitely circumscribed area of haziness about 5 cm. in diameter, occupying the posterior portion of the lower end of the left femur

and apparently extending through the periosteum. Bone formation was not evident. Giant cell tumor was suspected, and, at operation, a pocket containing a "quantity of reddish fatty material suggestive of blood clot" was found, and treated by thorough curettement. Convalescence was uneventful, but the tumor recurred locally in a short time and in six months the patient died with clinical signs of widespread metastasis.

Pathologic Examination.—Histologically, sections taken from different portions of the tumor (figs. 19 and 20) showed a loose, spongy stroma composed of

Fig. 18 (case 6).—Lateral view of left knee showing a lesion, indicated by the arrows, in the lower posterior portion of the femur; the ill-defined, noncircumscribed area of slightly increased density apparently extending through the periosteum posteriorly is not the picture of giant cell tumor; histologically, this case proved to be an osteogenic sarcoma which secondarily contained giant cells of the epulis type.

irregular sized and shaped cells, many of which were undergoing cell division. Some of these cells approached giant cell size but contained only one large, hyperchromatic nucleus. No supporting reticulum was present. Scattered diffusely throughout the growth were seen giant cells of the epulis type, containing from ten to forty small, oval, centrally placed nuclei. Here and there small foci

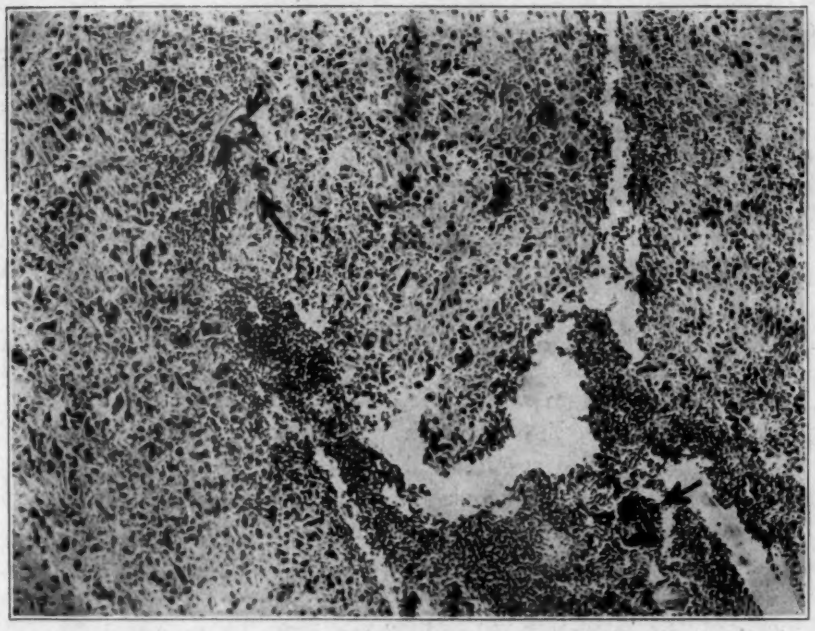

Fig. 19 (case 6).—Osteogenic sarcoma secondarily containing giant cells of the epulis type; two foci of bone formation may be seen near the area of hemorrhage; numerous osteoclasts are recognized in the cellular stroma; × 115.

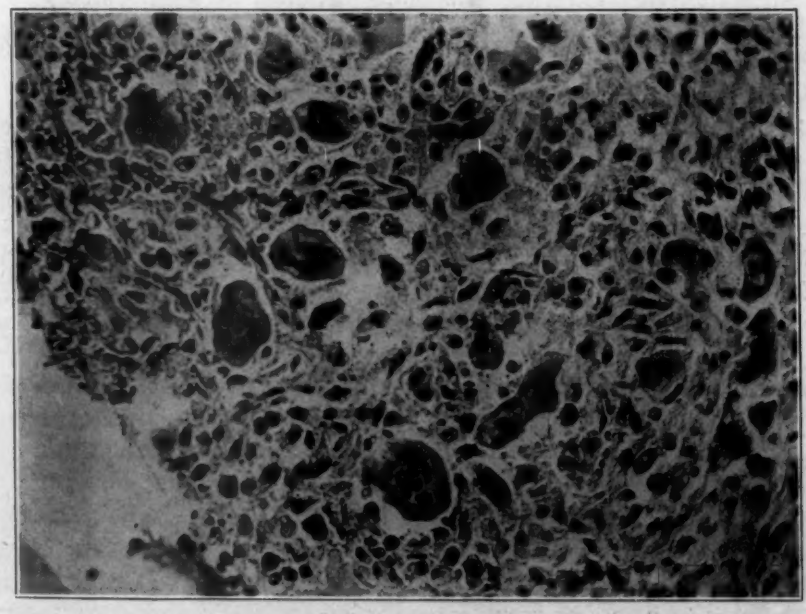

Fig. 20 (case 6).—Same sarcoma as shown in figure 19 showing numerous giant cells of the epulis type scattered throughout the stroma, which is composed of actively growing pleomorphic cells; the osteoclasts obscure the picture until the stroma is analyzed; × 275.

of calcification and ossification were demonstrable. Microscopically the picture was that of an osteogenic sarcoma containing giant cells of the epulis type, rather than a giant cell tumor that had undergone malignant change. Dr. James Ewing concurred in this diagnosis.

This case is confusing. Occurring in a young adult in a site frequently elected by giant cell tumors, this neoplasm gives the rather striking history that it has from the outset grown quite rapidly. The roentgenogram is both indefinite and atypical, and although the gross appearance of the lesion suggested that it might be of innocent nature, histologic study shows clearly that the tumor is basically malignant. The occurrence of numerous innocent appearing, multinucleated giant cells of the epulis type throughout the growth further obscures a picture that is already generally atypical and is significant in indicating the bone absorption activity of the neoplasm. Proper evaluation of the nature of the growth, however, is arrived at by a critical analysis of the stroma, and evidences of malignancy are recognized in its abundance of actively growing cells and in the many tiny centers of bone formation scattered throughout. Confirmation of this diagnosis is proved by a fatal outcome shortly after operation.

COMMENT

These cases are sufficiently varied that certain helpful points can be gleaned from their study, even though generalizations are not warranted. They illustrate well some of the difficulties that are likely to be encountered in dealing with central bone tumors in arriving at a correct diagnosis on which proper treatment and prognosis depend. A carefully taken history, thorough clinical study and critical roentgen-ray examination in the majority of instances establish fairly definitely and accurately the general nature of the growth, but microscopic analysis, we feel, offers the surest criterion of the specific nature and relative malignancy of the tumor. It is hardly necessary to add that a rigid and frequent "follow-up" of any bone lesion is imperative, if we are to be finally checked on our impressions regarding bone tumor behavior.

The histologic structure of the giant cell tumors gives one a rather definite criterion of the neoplasm's relative aggressiveness. An analysis of the stroma, with particular attention to its cellularity, cell type and cell activity, permits one to estimate fairly accurately the degree of malignancy any given tumor may possess. The more cellular stromas, composed of fibroblastic or spindle cells, and showing cell division stages, can be said to grow considerably more rapidly than the relatively acellular adult fibrous ones lower down the scale. In this connection, it is interesting to note that recurrent growths practically always present a noticeably more malignant appearing stroma microscopically than the primary growth exhibited, the increase in stroma cellularity and activity being a fair measure of the recurrent tumor's increase in virulence.

The giant cells of the epulis type that are characteristically present vary considerably in number in different tumors and, as a rule, are relatively less abundant in tumors possessing the more cellular stromas. Their main function, apparently, is that of bone absorption, for which reason they may be properly designated osteoclasts, a term introduced by Kölliker.[17]

Our interpretation of the histogenesis of the giant cell tumor is that two mesoblastic tissues, the osteoblastic, or osseous tissue proper, and the fibroblastic, or specialized fibrous tissue framework, intimately associated in bone structure, as pointed out by Stewart,[18] are the elements composing giant cell tumor. Study of the osteoclasts in their various stages of formation, best observed at the margin of the expanding tumor, suggests that they are derived from the osteoblastic element. Formed by the fusion of modified osteoblasts, or liberated and hypertrophied bone cells, as advocated by Kölliker [17] and Gross,[6] and possessing the faculty for further hypertrophy and multiplication, their variation in size, number and distribution in different tumors can be accounted for. Many of these modified osteoblasts, or liberated bone cells, fail to eventuate into giant cell formation and are recognized as the rounded and polygon shaped cells (figs. 5 and 9) embedded in the stroma along with the osteoclasts, this often giving an increased but pseudocellularity (fig. 8) to the stroma, which is likely to be misinterpreted. The osteoclasts, by virtue of their function and origin, have direct connection with tumor occurrence and in a sense may be regarded as specific neoplastic giant cells, but we consider them as being essentially innocent.

To the fibrous supporting reticulum and fibroblastic cells that constitute the stroma of giant cell tumor, we would ascribe origin from the specialized fibroblastic tissue, and we feel that the behavior of this structure governs the course of the growth. Such a conception would explain the innocence of a tumor with adult stroma at the lower end of the scale and the relative malignancy of the more cellular and immature stromas higher up, and is in keeping with the spindle cell or fibrosarcomatous picture that the majority of malignant growths have presented. In the rare instances in which osteoclasts were demonstrable in pulmonary metastases, their occurrence might be accounted for on the assumption that they were transported there by the metastasizing fibroblastic tissue.

A study of the behavior and course of the giant cell tumors emphasizes the fact that this bone lesion, whatever its true nature, possesses

17. Kölliker, A.: Handbuch der Gewebelehre des Menschen., ed. 6, Leipzig **1**: 347-350, 1889.

18. Stewart, M. J.: The Histogenesis of Myeloid Sarcoma, Lancet **2**:1106, 1922.

certain attributes that are recognized as features of tumor growth. Varyingly aggressive, it frequently exhibits its power of recurring locally after operative treatment and occasionally, particularly following pathologic fracture, its faculty for progressive, unlimited growth to the extent of invasion and destruction of nearby tissues is evident. In addition to this, it seems inescapable that this tumor may rarely actually metastasize, proof of which is offered in the cases cited in this study, and in references to other authentic cases. A lesion possessing such faculties should be regarded, it would seem, as a true neoplasm rather than a chronic inflammatory process and, although usually benign, as being always locally aggressive and in a sense potentially generally malignant. This conception establishes the guiding principle that giant cell tumors should be thoroughly eradicated as early as possible and at the first treatment, lest inadequate or improper treatment, whatever the choice, result in a local recurrence or perhaps in a malignant transformation of the growth.

SUMMARY

1. The known behavior of the giant cell tumor warrants its being classified as a true neoplasm.

2. The giant cell tumors constitute a series. Those at the lower end of the scale possess relatively adult fibrous stromas and are essentially benign. They exhibit more cellular and active stromas, composed chiefly of relatively immature fibroblastic cells and become increasingly more locally aggressive as the scale is ascended.

3. Under the stimulus of inadequate or improper treatment, they may recur locally, those at the upper end of the scale being especially liable to this tendency. Such recurrences, as a rule, are more aggressive or virulent than the primary growth, both clinically and microscopically.

4. They are potentially malignant and may as a result of repeated or improper treatment excitation on rare occasions undergo malignant transformation and metastasize.

5. The giant cells, or osteoclasts, that are characteristically present function as bone absorbers, and are of osteoblastic origin. They are not reliable indexes of the neoplasm's relative malignancy.

6. The stroma is of fibroblastic origin and its behavior governs the course of the giant cell tumor. Thorough microscopic study of its cellularity, cell type and cell activity offers a fairly reliable criterion of the innocence or relative malignancy of the growth.

7. History, thorough clinical and roentgen-ray study, macroscopic and critical microscopic analysis, and a rigid follow-up are all necessary in establishing the final correct diagnosis and the true nature and behavior of the giant cell tumor.

THE REGENERATION OF THE LYMPHATICS*

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That lymphatics exist in new growths and newly formed tissues has been shown by injection experiments. That they regenerate in normal tissues was mentioned by the late Professor Halsted [1] in 1922 in his article concerning the replantation of limbs in animals. His statement was based on the experiments included in this article.

Probably the earliest observation on the regeneration of the lymphatics was made by Krause [2] in 1863. By making colored injections in the skin adjacent to tumors he demonstrated the continuation of true lymphatics into the tumors.

In his lectures on surgical pathology and therapeutics, Billroth [3] in 1863 demonstrated specimens in which the lymphatics did not grow across scar tissue, at least not in early stages. After a 7 day old wound in the lip of a dog had healed by first intention the lymphatic vessels were injected. He said,

> You see that the young cicatrix, on the seventh day, when it still consists almost exclusively of cells, has no lymphatic vessels; these cease immediately at the young cicatrix; they do not form in the cicatrix until the fibrillary connective tissue bundles form. The granulation tissue also has no lymphatic vessels; where the inflammatory new formation, where the primary cellular tissue forms, the lymph vessels are mostly closed, partly by fibrous coagulations, partly by new cell formations. These observations have also been confirmed quite recently by Lösch of St. Petersburg, by examination of traumatically inflamed testicles.

In Bartel's [4] treatise on the lymphatic system in Bardeleben's Handbuch, he states that "Talke found in pleuritic membranes, newly formed lymphatics and capillaries as well as large lymphatics and lymphatic plexuses; besides, he saw lymph spaces." He also states that Poirier and Moran were able to inject abundant networks of lymphatics in recto-uterine adhesions.

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*From the Department of Surgery, Johns Hopkins University Medical Department.

1. Halsted, W. S.: Replantation of Entire Limbs Without Suture of Vessels, Proc. Nat. Acad. Sc. **8**:185, 1922.

2. Krause, W.: Ueber Lymphgefasse im geschwulsten, Deutsch. Klinik. **15**: 377-378, 1863.

3. Billroth, T.: Die allegemeine chirurgische pathologie und therapie, Berlin, 1863, p. 90, figure 11.

4. Bartels, Paul: Das lymphgefasse system, Jena, 1909, no. 17, Handbuch de anatomie des Menschen, herausgeg, von Karl V. Bardeleben.

Bayer [5] attempted to show by experiments on dogs that lymph glands recurred after their extirpation. By injecting limb lymphatics with india ink the axillary lymph nodes were demonstrated and were then excised. After stated intervals the limb lymphatics were again injected with cinnabar, and then the entire axillary contents removed and sectioned. In one animal no lymph nodules were found. In another a small, soft pea-sized gland containing cinnabar was the only evidence of lymph nodes. As some of the axillary fat was stained red he concluded that lymph glands recur from the surrounding fat. On the basis of these experiments, together with certain pathologic material, he developed the theory that lymphatic glands were formed from fat and that fat was part of the lymphatic system.

About the same period Delius [6] conducted the experiments which led him to believe that regeneration took place when portions of a gland were excised. Ribbert [7] also believed that regeneration followed excision of portions of the submaxillary lymph gland.

Heuter [8] and later Meyer [9] were unable to find any experimental evidence of regeneration in glands and the latter found no recurrence following the extirpation of the popliteal glands. Meyer suggested that following the resection of mesenteric glands, the reestablishment of lymphatic connections with the receptaculum chyli was probable but not proved. He therefore attempted to test the question of regeneration of lymphatic vessels by ligating and dividing the main lymphatic trunks lying on either side of the saphenous vein, near the knee of the dog. In eight cases studied, fourteen to ninety-one days after operation, injections showed no regeneration of these vessels. He concluded that if stasis were the main stimulus to regeneration it was quite probable that resection and ligation of one or two principal trunks in the region of the knee and elbow did not interpose sufficient obstruction to the flow of lymph.

Coffin [10] brought a loop of intestine outside the abdominal wall. Ten days later the lymphatics of the loop were injected and new lymph

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5. Bayer, Karl: Ueber regeneration und neubildung der lymphdrusen, Ztschr. f. Heilk. **6**:105, 1885.

6. Delius: Ueber die regeneration der lymphdrusen, dissertation, Bonn, 1888, quoted by Meyer, A. W.: An Experimental Study on the Recurrence of Lymphatic Glands and the Regeneration of Lymphatic Vessels in the Dog, Bull. Johns Hopkins Hosp. **17**:185, 906.

7. Ribbert: Beitr. z. path. anat. u. allg. path. **6**, 1889, quoted by Meyer (footnote 6).

8. Heuter: Verhandl. d. deutsch. path. Gesellsch. f. Chir., 1904, quoted by Meyer (footnote 6).

9. Meyer (footnote 6).

10. Coffin, T. H.: On the Growth of Lymphatics in Granulation Tissue, Bull. Johns Hopkins Hosp. **17**:277, 1906.

vessels could be seen in the granulation tissue surrounding the intestinal loop. Thus it seemed conclusive that lymphatic channels had grown into the overlying granulation area from the lymphatics of the intestinal wall.

Evans [11] in 1908 reported the growth of lymphatics into malignant tissue, a metastatic sarcomatous nodule in the intestinal wall. He injected the intestinal lymphatics and found the delicate lymph channels of the nodule in direct connection with the preexisting and neighboring lymphatic plexus. The newly formed lymphatics seemed to be capillaries and to have arisen from the mucosal system.

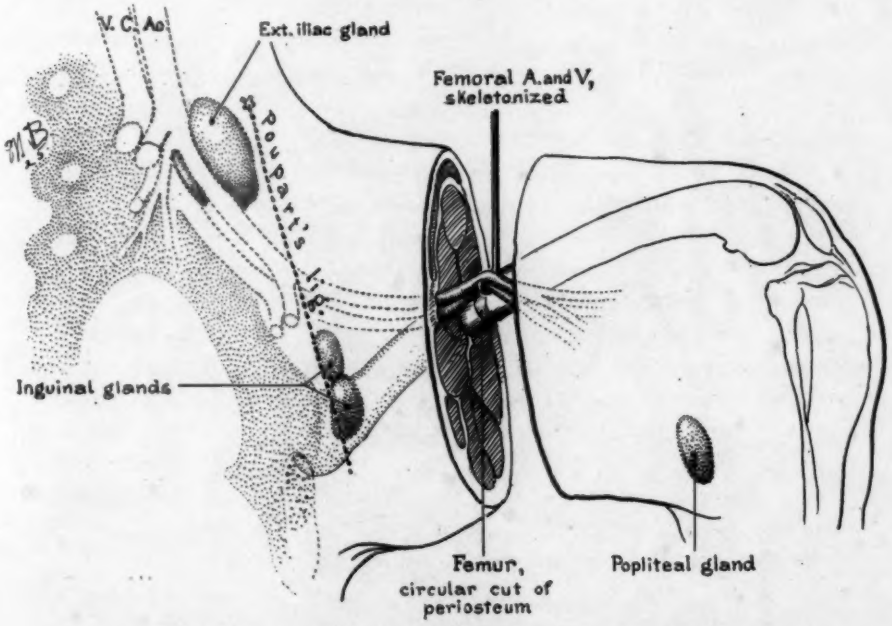

Fig. 1.—Division and isolation of structures in the replantation of a dog's thigh.

When inquiring into the cause of edema of transplants of skin and soft parts Eloesser [12] expressed the view that scar tissue caused edema by blocking the lymphatics. He made incisions across the dorsum of a rabbit's ear. The wound, which extended down to the broad cartilage, was allowed to heal by granulation. Although barium sulphate injections did not pass beyond the scar, small lymphatics could be traced across

11. Evans, H. M.: On the Occurrence of Newly Formed Lymphatic Vessels in Malignant Growths, Bull. Johns Hopkins Hosp. **19**:232, 1908.

12. Eloesser, Leo: Obstruction to the Lymph Channels by Scar, J. A. M. A. **81**:1867 (Dec. 1) 1923.

the wound in some instances when injections were made with india ink. This obstruction by scar tissue persisted as long as four months.

OPERATIVE PROCEDURE

Our experiments on the regeneration of lymphatics developed incidentally during attempts to produce experimental elephantiasis chirurgica in dogs.[13] One of the procedures suggested by the late Professor Halsted for this study was replantation of a dog's hind limb. It was then possible to determine the degree of swelling which resulted from the

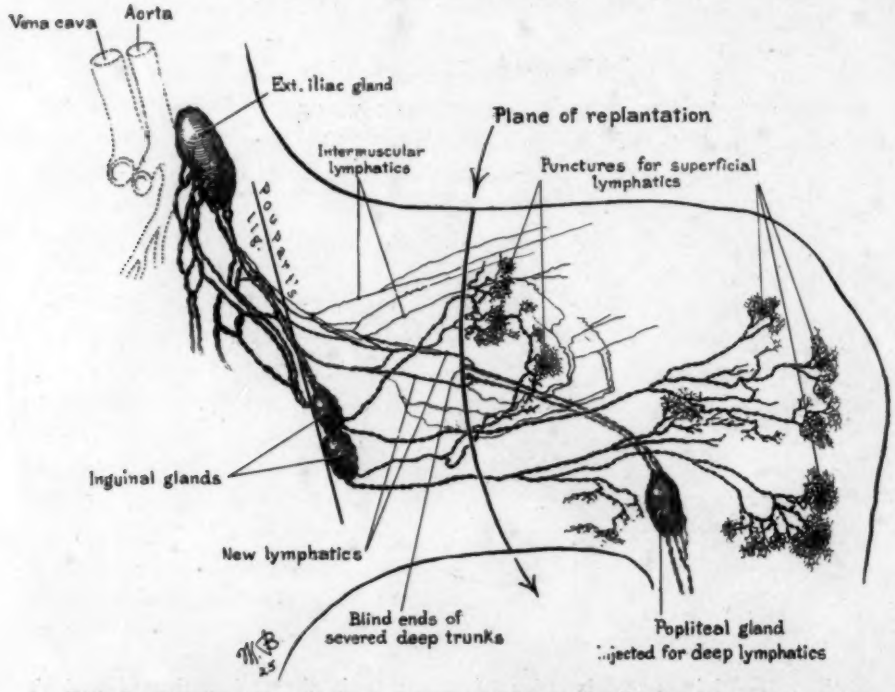

Fig. 2.—Regeneration of both the superficial and deep lymphatic sets after replantation of a dog's thigh (drawing of figure 3).

division of vessels and lymphatics. By a complete circular incision through the middle third of the thigh, the skin, subcutaneous tissue and muscle were divided transversely (fig. 1); only the femur, the femoral artery and vein were left intact and these remaining structures were carefully isolated and stripped of all areolar tissue. A circular cut was made through the periosteum and the outer part of the adventitial coat of the femoral vessels. This insured complete severance of all

13. Halsted, W. S.: The Swelling of the Arm After Operations for Cancer of the Breast—Elephantiasis Chirurgica—Its Cause and Prevention, Bull. Johns Hopkins Hosp. **32**:309-314 (Oct.) 1921.

lymphatic vessels. The extremity, which had thus been practically amputated, was replanted by careful approximation of the muscle stumps and skin edges with silk sutures. These replanted limbs united without infection and with the least possible scar tissue, as shown by histologic study. In no instance was there any sign of gangrene. Because of the excellent healing of the severed tissues the regeneration of the lymphatics could be studied for probably the first time under what may be considered normal conditions. Moreover, in our procedure the division of all lymphatics to the limb removed the difficulty experienced by Arthur Meyer when he was unable to produce sufficient stasis to demonstrate the regeneration of lymphatic trunks.

LYMPHATICS OF THE EXTREMITY

Normally there are two sets of lymphatics in the extremity, superficial and deep. These arise in the embryo [14] from the primary iliac sacs which are dorsolateral to the aorta. The posterior trunk of these sacs gives off one large branch (the common iliac) which soon breaks into a hypogastric or internal iliac trunk and an external iliac or femoral trunk. The latter drains the two sets of lymphatics from the hind limb. In the embryo the external iliac trunk sends a few lateral branches with the sciatic artery; it then divides into a caudal and a medial group, the latter forming the inguinal lymphatics, which drain a plexus along the inguinal ligament. This plexus is converted into elongated lymph nodes which separate into deep and superficial groups draining the lower abdominal wall, external genitalia, perineum, mesial side of the thigh and practically the whole of the lower extremity. The remaining vessels of the external iliac trunk continue caudally and follow the femoral artery in its course to the thigh. A popliteal gland becomes differentiated and drains most of the lymphatics of the lower leg and foot. The posterior trunk of the primary iliac sacs is differentiated into lymph nodes which are situated about the iliac vessels and the terminal portion of the abdominal aorta.

The lymphatics of the deeper set were first clearly demonstrated by Aagard [15] in 1913. The lymphatics of the muscle and muscle sheaths injected with prussian blue form networks in the muscle sheaths and unite to form larger vessels that drain into the regional lymph glands.

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14. Sabin, Florence R.: The Origin and Development of the Lymphatic System, Rep. Johns Hopkins Hosp., 1913. Reichert, F. L.: On the Fate of the Primary Lymph Sacs in the Abdominal Region of the Pig, and the Development of Lymph Channels in the Abdominal and Pelvic Regions, Contributions to Embryology no. 58, 1921, p. 17-39, Carnegie Inst. Washington pub. 276.

15. Aagard, O. C.: Ueber die lymphgefasse der zunge, des quergestreiften muskelgewebes und der speicheldrusen des menschen, Anatomischer heften von Fr. Merkel und R. Bonnet, 1913, vol. 47, pp. 602-620.

Fig. 3.—Cleared specimen of a replanted thigh, showing the regenerated lymphatics in black and the arterial system in white.

In the adult animal, therefore, most of the superficial lymphatics of the leg and foot, as well as some of the deep lymphatics that drain the muscles of the leg terminate in the popliteal lymph gland. From this gland large efferent trunks course along the femoral vessels to end in the external iliac glands just distal to the trifurcation of the aorta. Many of the superficial lymphatics of the thigh and upper leg drain into the inguinal lymph glands which in turn have efferent vessels terminating in the external iliac glands. The deeper set of lymphatics in the muscle sheaths of the thigh eventually enter trunks that accompany the main femoral lymphatics and drain into the large external iliac glands.

METHOD

In the limb replantation experiments it was comparatively easy to follow the regeneration of both the superficial and deep sets of lymphatics. Of the various methods for their demonstration methylene blue and india ink were found to be most satisfactory. Barium, thorium and bismuth, and other substances, by which the lymphatics might well be outlined through the roentgen rays, were repeatedly tried but, unfortunately, no satisfactory technic could be developed for obtaining convincing roentgenograms. The india ink method proved to be excellent not only for dissections immediately after the injection, but also for making permanent cleared specimens. It was thus possible to demonstrate the smallest lymphatic channels.

Several hours before the animal was sacrificed, diluted india ink was introduced into the foot pads and into the skin of the leg and thigh distal to the operative line and also into the popliteal lymph gland. The animal was then killed with ether.

In some cases the arterial system also was injected using the white bismuth roentgen-ray mass of Hill.[16] Unless a dissection was made immediately, the entire thigh and tissues of the pelvic floor, including the pelvic lymph glands, were removed en bloc, hardened in formaldehyde and cleared by the Spalteholz method as modified by Sabin.[17] In these cleared specimens the black lymphatic vessels stood out sharply in the nearly transparent tissue. A striking contrast was presented by the arterial tree outlined by the white bismuth mass and the black lymphatics filled with india ink (fig. 3). Specimens were made at varying intervals (two days to fourteen months) after operation.

16. Hill, E. C.: Notes on an Opaque X-Ray Mass, Bull. Johns Hopkins Hosp. **35**:218 (July) 1924.

17. Sabin, Florence R.: On the Fate of the Posterior Cardinal Veins and Their Relation to the Development of the Vena Cava and Azygos in the Embryo Pig, Contributions to Embryology, 1915, **33**, Carnegie Inst. Washington pub. 223.

LYMPHATIC REGENERATION

The earliest specimen showing regeneration of the lymphatics was four days after operation. This regeneration occurred in the superficial set of lymphatics and consisted of three or four areas at the line of skin division where healing was proceeding in the well approximated skin edges. In these few areas, tiny black lines extended from the distal injected lymphatics to the severed skin edge, crossed and converged again to enter a single lymphatic on the proximal side where they continued to the inguinal lymph gland, staining it black. Elsewhere the superficial lymphatics were injected only to the replantation line.

This regeneration takes place first in the superficial set and in the areas of careful approximation of the skin edges with healing by first intention. Where there is any appreciable scar, or where healing has been interfered with by trauma, foreign body or infection, the growth of lymphatics across that region may be delayed for weeks or months, even as Billroth observed years ago in his experiments on the lip. Only after many such replantation operations with utmost vigilance as to aseptic precautions, control of hemorrhage, gentle handling of tissues and careful and accurate approximations—all of these the basic principles of Professor Halsted's teaching—did sufficient operative skill develop for the demonstration of lymphatic regeneration at the early period of four days.

The deep set of lymphatics was first demonstrated to show regeneration in a specimen made eight days after replantation. Both the superficial and deep sets were injected. The intradermal ink injections showed the superficial lymphatic system as tiny tortuous black lines just beneath the skin extending to the line of union of the circular skin closure where, in various areas, arborizations appeared and extended across the wound to form on the proximal side a converging fan of tiny vessels drawn into larger channels to the inguinal lymph glands (figs. 2 and 3). This bridging of the wound by new or regenerating lymphatics occurred at sites where the primary wound healing had the least amount of reaction and scarring. In the deeper lymphatic set the areas of regeneration were not as numerous. From the popliteal lymph gland small black vessels coursed for a distance with the blood vessels. As they approached the replantation line ramifications were found between the muscle groups, in the intermuscular septums, and in the muscle sheaths which finally crossed the wound as minute branches, continued for a distance in the muscle sheaths, then united with others into one or two main femoral lymphatic trunks which emptied into the large external iliac glands. That these iliac glands were not blackened by ink from the inguinal glands was ascertained by injecting only the deep set in another animal.

In specimens in which the lymphatic injections were made from two, three to twenty weeks after replantation the main lymphatic trunks had frequently reunited, occasionally without any evidence of their point of division or else with an irregularity and kinking in the vessels at this point.

In figures 2 and 3 the superficial lymphatic set of an eight day specimen has been added to the drawing which showed only the lymphatics of the deeper set made from the cleared specimen of the left thigh of a dog thirty days after replantation. The black vessels are lymphatics and the arterial system is white, as outlined by Hill's bismuth mass. Some back flow of ink from the iliac glands into a few branches from the pelvic region is shown in the illustration. Adjacent to the trifurcation of the aorta lie the iliac glands darkened with ink. The skin is not included in the drawing but the lymphatics of this superficial group are shown as strong black lines coursing over the popliteal lymph gland, which was injected with ink, to the two inguinal glands. The femoral trunk lymphatics follow the blood vessels to the operative line, but a number of small branches ramify through the deeper intermuscular septums to cross the replantation area where they unite with other deep lymphatics that eventually drain into the iliac gland.

POSTOPERATIVE EDEMA

That the lymphatics play a rôle in the postoperative edema in this type of operation is evident, though it is not possible to determine the relative importance of either the venous or lymphatic systems in its production.

Following replantation, swelling of the limb distal to the suture line begins on the second day, reaches a maximum, as indicated by measurements, on the fourth or beginning of the fifth day, and has subsided completely by the seventh or eighth day. In another report it will be shown that while the growth of the arterial vessels across the operative field occurs about the third day, the venous and lymphatic channels have not regenerated until the fourth day when the subsidence of the edema is just beginning.

The operative procedure has, therefore, disturbed the circulatory balance between the arterial system in the one direction and the lymphaticovenous system in the other. Once the limb has reached its maximum swelling or is just commencing to subside the only patent venous channel, the femoral vein, can be ligated with impunity, since neither gangrene will ensue nor further edema occur. In fact, the delay in the subsidence of the edema will be only one or two days.

From these observations and injections it seems clear that in the fourth and fifth days after replantation the venous regeneration is much

more abundant than the lymphatic, the latter as yet having little effect on the edema.

No change whatever can be seen in the limb if the femoral vein is ligated after seven or eight days, when the subsidence of the swelling has just been completed. If, however, the lymphatics are blocked with india ink granules at this time, the edema reappears. It would seem that the lymphatic system with its regeneration has a relatively important rôle in bringing about the subsidence of the edema at this stage.

Repetition of this experiment several days later, on the tenth and twelfth days, again shows that ligation of the femoral vein leads to no change in the limb distally, nor does blockage of the lymphatic vessels at this time lead to edema. Now apparently the new venous channels are functioning adequately.

PRACTICAL SIGNIFICANCE OF THESE EXPERIMENTS

The importance of the lymphatic system in the spread of cancer cells has been recognized for many years. With this knowledge of cancer extension along lymphatic channels the so-called radical operation was developed in which not only the primary growth but also the adjacent tissue over a relatively large area and the regional lymph glands were removed en bloc.

In certain regions of the body, particularly about the mouth and jaw, some surgeons have divided the operation into two stages. The aseptic part of the operation is done first; namely, the block dissection of the cervical lymph nodes. On the healing of this aseptic wound in one or two weeks, the second stage is performed by either removing the primary growth surgically or treating it with radium.

Although this manner of radical treatment has certain advantages in securing better wound healing, it does introduce the question of possible regeneration of lymphatic channels between the first and second stages. Since it has been shown that lymphatics do regenerate in less than a week such an operative procedure in the radical treatment of cancer would be dangerous.

SUMMARY

Regeneration of lymphatics has been demonstrated under conditions closely approximating the normal. The results are based on injection experiments in replanted limbs of dogs.

New lymphatics are shown to cross a scar as early as the fourth day and by the eighth day the regeneration is physiologically adequate in both the deep and the superficial sets of lymphatics.

Concurrent experiments have shown that compensatory arterial and venous regeneration occur by the third and fourth day, respectively.

Stasis of the lymphaticovenous system provides a stimulus for the regeneration of both groups of lymphatics.

Proof is advanced that the lymphatics play an important rôle in assisting the veins in overcoming edema and restoring a limb to its normal condition.

Study of the postoperative edema following replantation of the limb leads to a better understanding of such postoperative changes as edema and induration of the skin and subcutaneous tissues after dissections of the glands of the neck.

These studies on lymphatic regeneration offer reasons for surgical procedures in treating malignant conditions; namely, the primary growth should be removed before or at the same time as the regional glandular dissection. If, as is sometimes practiced, the clean operation of removal of glands is done a week or more before the primary growth is excised, sufficient time will have elapsed for the regeneration of new lymphatic channels.

INTESTINAL OBSTRUCTION

A SURVEY OF 135 PERSONAL CASES

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The mortality in surgical cases of intestinal obstruction is entirely too high. Reports show that it is 30, 40, 50 per cent, and even higher. There is no phase of abdominal surgery that offers so great opportunity for improvement in its results as that of intestinal obstruction. The mortality in operative cases should not be more than 5 or 10 per cent. In order to obtain this end, no great skill is required, or no expensive outlay in apparatus is demanded. We have only to apply a few simple principles of diagnosis and treatment to reduce the death rate for obstruction of the bowels to one-fourth its present surgical mortality. Seventy-five per cent of the deaths after operation are due to late operations. The fate of the patient is determined by the treatment of the first physician that sees him. Quite invariably the sufferer from ileus sends early for a physician; hence the responsibility for success or failure lies entirely on the shoulders of the medical profession. These patients suffer so severely that they do not delay in seeking relief.

In this article we shall not stress the matter of diagnosis, but rather that of the treatment in the hands of the surgeon after the patient comes to the hospital. However, a few brief remarks in the matter of diagnosis will not be out of place. There are five cardinal points in the symptomatology in making a positive diagnosis of intestinal obstruction:

1. Pain, which is of sudden onset, severe and crampy in character.

2. Vomiting, at first reflex, then due to an overflow from reverse peristalsis (but the diagnosis should be made before this overflow occurs).

3. Blocked bowel, in which it is possible to obtain either fecal matter or flatus by the enema. However, the bowel may move once or twice below the obstruction, but following this there is absolute block of the bowel.

4. Visible peristalsis, which can be seen in the majority of cases early, even three or four hours after the onset of the obstruction. This, when observed, in connection with the other four cardinal symptoms is absolutely pathognomonic. It may require an hour or more of careful watching under a good light in order to observe the peristaltic waves. It is a sign well worth looking for. It is an early, rather than a late sign. It will not be seen after distention has taken place.

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* Read at the Pacific Coast Surgical Association Meeting, Del Monte, Calif., Feb. 26-27, 1926, illustrated by motion pictures.

5. No fever. There is generally a wrong impression in regard to the temperature in acute ileus. Of course, just before death, there may be some fever, but for the first forty-eight hours there is no rise in the temperature, at least not over half a degree above normal.

There are other signs, symptoms and methods of making a diagnosis, but they are relatively unimportant, and may only serve to confuse us. These five points we have mentioned are sufficient to make a diagnosis of intestinal obstruction. We believe it is possible to recognize acute ileus with more accuracy than appendicitis, gallstones or gastric ulcer. But in order to have these five cardinal signs and symptoms of any importance there are two vital things that must be constantly carried in mind. First, there shall be no hypodermics of morphine given. The majority of patients with intestinal obstruction have one or more hypodermics of morphine administered them by their physician before they are seen by the surgeon. The use of morphine in these cases renders a positive diagnosis only probable, and will likely delay the operation from twelve to twenty-four hours or longer. Second, the administration of cathartics either by the patient's friends or by the physician is purely barbarous and unjustifiable. Four-fifths of the mortality of operative cases of intestinal obstruction can be directly attributed to the administration of morphine and cathartics. The profession has been altogether too slow to recognize the viciousness of these two classes of drugs in all acute painful diseases of the abdomen. Their exhibition in the cases of intestinal obstruction is deadly. The harm that comes from their use may be well illustrated from our own experience of 135 operative cases of acute ileus. Eighty-four of these patients were referred to us; that is, they were examined by some other physician before they were seen by us. Of these eighty-four, twenty-three died, a mortality rate of a little above 27 per cent. Not all of these eighty-four patients had been given cathartics or morphine, but the great majority of the *fatal* cases had been thus treated. Fifty-one of these were patients that were seen only by my associate, Dr. Moran, or myself before operation. Of these fifty-one, three died, a mortality of 6 per cent. None of these fifty-one had any morphine or cathartics given before diagnosis.

In the year 1925, we had twenty-three cases referred, with only three deaths. This may indicate that if surgeons maintain a campaign of education as to the dangers of morphine and cathartics, it may result in lowering very materially our death rate.

We will omit the discussion of differential diagnosis, and we will not try to solve the problem of what causes death in ileus. In the hands of the average surgeon, if operation is performed early the death rate need not be more than 5 or 10 per cent.

A brief review of the technic of treatment follows: An early operation within the first twelve or twenty-four hours after the onset of the

obstruction is imperative. An ample midline incision, extending from the pubes to above the navel, should be made. Evisceration of the obstructed bowel is quite necessary. This may appear to be a vicious procedure. It is contrary to our previous conception of good abdominal surgery. We have instinctively avoided removing the intestines from the abdominal cavity. We have been fearful of shock. Our anesthetist is frequently asked to note if there is any change in the quality or rate of the pulse while the intestines are eviscerated, as we do it. Rarely does she report any change of any importance whatsoever. The intestines, as soon as they are removed from the abdomen, are kept warm by large, hot, salt napkins (water 110 F.). These salt napkins are constantly replaced as they become cool. Traction on the mesentery is avoided, since it is painful and will cause some shock. With the bowels eviscerated, it is very easy to locate the site and cause of the obstruction. Before operation we make no effort to determine the location or nature of the obstructing cause.

It is immaterial to speculate on where the obstruction is or what is causing it. It is quite sufficient to determine that somewhere by some cause there is a mechanical block of the bowel. We can quickly and easily recognize its site and nature after the abdomen is open. As soon as it is found, the obstruction is relieved. But should we stop here, in the majority of our cases, we have only half completed our task. From causes undetermined, the contents of the bowel are very detrimental to the patient. It seems to be extremely toxic. To leave these imprisoned contents in the bowel is to subject the patient to unnecessary hazard of absorption of toxic material. We must remember that the bowels will not move for perhaps two or three days or more following the operation.

The following is the method that we use in emptying the bowel of its imprisoned contents above the obstruction: We take a large size test tube, with a good flange at the top, and cut off its closed end. Over this is fitted a large rubber tube not to exceed 2 feet in length. At some point in the bowel near the obstruction (just below it if possible) an intestinal clamp is placed. After a purse string Lambert linen suture has been inserted surrounding the site of our intended incision, a longitudinal opening is made into the bowel. We use rather heavy linen for this suture. Then the free end of the test tube is inserted into the bowel, and the purse string suture drawn taut around the flanged end of the test tube. Only the first half of the knot is tied. The suture is then clamped tight to the tube by hemostat. An intestinal clamp is placed distal to this tube. The test tube and the rubber tube connected to it are given to an assistant or nurse. My hands are well anointed with sterile petrolatum. Beginning just as near the upper end of the jejunum as possible, an assistant rapidly pulls the intestines through my petrola-

tum anointed fingers, thus stripping out all of the intestinal contents, which are discharged through the test tube and rubber tube into a basin, held outside of the operating field. The assistant uses gauze in his hands and rapidly draws the intestine through my fingers from the upper jejunum to the test tube. Occasionally we go over these intestines the second time, thus completely removing all contents of the bowel above the obstruction. The intestines are flat, ribbon-like, when we finish. The whole procedure can be done in five or ten minutes. Frequently we are able to take two, three, four or five quarts of foul smelling contents from the obstructed bowel.

The rubber tube connected on the test tube must not be too long. If we have it long enough to reach the floor, we have a siphon effect that will generally aspirate into the tube the opposite wall of the intestines, thus defeating our purposes. By having a short rubber tube, and instructing the nurse to hold it nearly horizontal, we obviate this disagreeable feature.

Emptying the intestine is a life saving procedure in these cases. We may wash the stomach while the patient is on the table—not always, however. Before we instituted this method of emptying the bowel, our patients with obstruction would vomit most furiously for two or three days following the operation. In fact, gastric lavage was the rule every two or three hours and the patients generally looked desperately ill. They were extremely toxic. One would hardy believe the improvement in the general condition of these patients that takes place by simply emptying the intestines, as we have described. We rarely use gastric lavage following the operation, and patients with obstruction have no more postoperative vomiting than an ordinary patient with appendix, gallbladder, stomach or pelvic disease. And their convalescence following operation is as uneventful and smooth as that of any other abdominal surgery. The operation should be done as expeditiously as possible—from thirty to forty minutes is ample time to carry out the procedure that we have mentioned. We use no drainage. Proctoclysis is the rule. Generally, we use salt solution, although if there is any acidosis, which sometimes occurs, we use soda. Morphine may be used postoperatively for twenty-four hours. No cathartic is given at all. The bowels will generally move of their own accord within four or five days after the operation. If they do not, an enema may be used.

Except for cancer of the large bowel, we never use temporary enterostomy. We feel that temporary enterostomy only empties a few coils of the intestines in the immediate vicinity, and the obstruction goes on the same as ever.

This article is based on the experience of 135 operative cases, twenty of these cancer of the large bowel, with seven deaths; thirty strangulated hernias (all varieties) with six deaths; postoperative adhesions (old),

forty-six cases with nine deaths; nine cases of postoperative adhesions (new), that is, those occurring in the hospital before discharge from the hospital, with no deaths (all of these were drainage appendix cases); twelve intussusception cases with two deaths; eight volvulus cases with one death; ten miscellaneous cases with one death; or a total of 135 cases with twenty-six deaths, a general mortality rate of 19.2 per cent.

The fatal cases include, of course, all those in which death occurred in the hospital from any cause whatsoever; also one patient that died of gangrene of the lung three weeks after the operation, ten days after he had returned home, and one patient with abscess of the lung due to an infected emboli from the abdominal wall. This man died six weeks after his operation, and a month after he had left the hospital. So we feel that the mortality rate is an accurate statement of the results.

SUMMARY

No morphine or cathartics should be given to any patient suffering from abdominal pain and vomiting. Pain, vomiting, blocked bowel, visible peristalsis and no fever are the five cardinal symptoms and signs of an obstructed bowel. Operation should be done the first twelve or twenty-four hours. The imprisoned contents of the bowel above the obstruction should be removed. The mortality can be reduced to less than 10 per cent.

By carrying out the principles enunciated here, one need have no more dread of intestinal obstruction than he would of gallstones, ulcers of the stomach or pelvic tumors. The operation and after-care will be no more difficult than in any other abdominal surgical procedure.

THE SURGICAL CONSCIENCE*

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I am deeply sensible of the great honor conferred on me last April at our organization meeting in electing me the first president of this association. I feel that there are many men on this coast who, by virtue of their long service to the profession and because of their contributions to surgery, are better qualified than I for this position, but I am sure there are none who are more sincere in their loyalty to the cause of surgery nor more enthusiastic in their faith as to the possibilities of this organization. I believe it marks an epoch in the development of surgery on the Pacific coast.

I have chosen as my subject for the first presidential address, the surgical conscience.

The all important part played by infection in surgery, as first pointed out by Lord Lister, early focused the efforts of surgeons on the development of aseptic technic. The term aseptic conscience came to have a very definite significance, not alone for surgeons but also for nurses and hospital attendants. It did much toward creating the esprit de corps of the operating room and stimulated all who had to do with surgery to practice that infinite care which we now recognize as necessary to successful surgery and which has become standardized in most hospitals.

The term, which played such an important rôle in the early days of surgery, is now rarely used, so common has the knowledge of bacteriology become and so well established is the theory of asepsis. Operating room technic for which the surgeon formerly felt himself responsible has now been committed largely to the nursing personnel of the operating room. Little is now left for the surgeon in preparing for an operation. Having properly prepared his hands, he enters the operating amphitheater with a clear conscience, confident that every precaution has been taken to prevent infection. He is now responsible for his technic alone. The highly trained surgical nurse has relieved him of all the important minutiae of asepsis. Even his operating technic, so far as asepsis is concerned, is safeguarded by the watchful, unobstrusive nurse who calls his attention to a torn glove, a contaminated instrument or a soiled dressing. We surgeons are prone to forget that much of our success depends on these conscientious, untiring and often poorly rewarded nurses.

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* President's address read before the Pacific Coast Surgical Association, Del Monte, Calif., Feb. 26 and 27, 1926.

But there is a much larger moral obligation on the surgeon than that which has to do with aseptic surgical technic as employed in an individual case. It is this larger obligation which I wish to emphasize at this first annual meeting of the Pacific Coast Surgical Association and to discuss under the name of the surgical conscience, the manifold relationships of the surgeon to his patient, his medical colleagues and to the community. I believe that such a discussion if frank and free will be profitable in clarifying our own minds on certain phases of our professional life and that by so doing we may point the way to the correction of some of the evils which have crept into our guild. As a result of these evils, the medical profession has lost prestige in the public mind and there is great danger, if they are not corrected by the profession itself, that it may sink into still lower levels of professional integrity and self respect.

The surgical conscience may be discussed under the following headings:

As related to the necessary preparation for the practice of surgery. Are we not as a profession encouraging half equipped and poorly trained men to undertake surgery? Our medical schools and our state laws, by virtue of their conferring and licensing powers, put the stamp of approval on the young practitioner and he is vested with both moral and legal authority to perform the most difficult and dangerous operations immediately on graduation.

Most of the older members of this association obtained their surgical experience and skill in the hard school of general practice. Few of us, I think, would assert that we have not sacrificed lives that might have been saved had we possessed better judgment and greater skill. This is true notwithstanding the fact that we did the best we could. Surgery has made such rapid strides in the last thirty years that it has been impossible to train men adequately and in sufficient numbers to meet the demands of the public. This necessitated the employment of poorly trained and self made surgeons. The broad background that the surgeons of the passing generation acquired in general practice and their brilliant achievements were in large measure due to their wide knowledge of general medicine.

It is no longer justifiable to rely on private practice for training in surgery; neither should we be satisfied with purely didactic and technical training, such as an apprenticeship in surgery affords. But a wise combination of both will insure the requisite technical skill and surgical judgment that should characterize the surgeon of the future.

There is now a surplus of surgeons in almost every community. Competition is now so keen that ambitious young surgeons with little practice and little experience are finding indications for surgery in a large percentage of the patients who consult them. It is the exception to find a woman over 40 who has not had one or more operations and

I am sure that all of you will testify that much of this surgery is ill advised and poorly executed.

What is the solution? I am not prepared to offer a satisfactory solution but I believe a quickened conscience and a concerted effort on the part of associations such as this can find a remedy. I believe that the ultimate solution lies in a special apprenticeship of not less than five years. The regular medical license should carry with it the right to practice only minor and emergency surgery. The commission on the improvement of medical education which has recently been organized will doubtless have some valuable recommendations to make on educational requirements for specialism. It is to make a comprehensive study of medical education extending over a period of five years and the personnel of the committee insures a comprehensive survey.

The second heading I would suggest for this discussion of the surgical conscience is, the care that should be employed in the selection of cases for operation. In no field of human activity is there greater need for a keen conscience and a trained judgment than in the practice of surgery. The most rigid checks are necessary if the patient is to receive just treatment. This is particularly true in the field of elective surgery. In traumatic and emergency surgery the indications for treatment are fairly definite and there is as much danger of erring on the side of conservatism as on that of radicalism, but in the great field of elective or doubtful cases, this is not so. Too often hasty diagnoses are made on insufficient evidence and too little time allowed for thorough preparation for operation. The surgeon is too often influenced by monetary considerations, by the fear of competition and by the opinions of the patient. Sometimes the surgeon's convenience, his vacation plans, his golf engagement or some other social affair will enter into the decision as to when an operation shall be done and may well be the determining factor in its outcome. Often a desire to save the patient expense and incidentally to conserve his resources so that he can pay a better fee will deter the careless and unscrupulous surgeon from resorting to all necessary diagnostic and preoperative precautions.

Routine preoperative preparation in every major operation, even in those patients who are apparently in good condition, I am sure, is commonly neglected and is the cause of many unnecessary deaths. Take, for example, the large group of cases in which there is a secondary anemia and dehydration. These patients, even to the experienced eye, look pretty well and the average surgeon will advise operation without thought of danger. If the blood is examined it will often show a hemoglobin around 50 per cent. The blood pressure will be 100 systolic, or less. Such a patient will probably survive a skilful, dexterous operation but the margin of safety is very narrow. The same patient after two or three days in bed with daily infusions of 2,000 cc. of salt solution and a blood

transfusion will so improve that even a blundering operation will be tolerated. The margin of safety can be still further increased by preparing for a postoperative transfusion should undue complications arise or the patient's condition prove unsatisfactory at the conclusion of the operation.

Another group of cases in which the most painstaking care is necessary, both preoperatively and postoperatively, if the best results are to be secured, is that class suffering from partial or chronic intestinal obstruction. Carefully taken roentgenograms to determine the site of obstruction and the amount of stasis, blood chemistry estimations to determine the degree of toxemia, thorough cleansing of the intestinal tract and the restoration of fluids are all preoperative measures of the greatest importance. Then the conscientious surgeon must face the necessity for two or more operations if he is to give the patient the maximum chance for recovery and restore the fecal current. He must be willing to face the criticism of the patient and his friends if a permanent fistula remains and he must have the courage to do no more at each operation than the patient can endure, even though it means weeks in the hospital with troublesome daily dressings, the abandonment of all thought of compensation, and even though a malpractice suit is staring him in the face at the end.

How often have we seen deaths following attempts at complete operations in resecting the bowel for chronic obstruction by inexperienced or conscienceless surgeons! How often have we cherished vain regrets at the fatal outcome of surgical operations or been tormented with the thought that we might have done better had we taken more time to study our cases, given more thorough preparation or exercised more patience and better judgment at the operating table! I believe that all of these factors should enter into the training of young men for surgery and that those of us who have to do with the instruction of these men should lay stress on the necessity of developing a surgical conscience, much as we emphasized in the beginning of the aseptic era the aseptic conscience.

Just as the technic of the operating room typifies the aseptic conscience, so the modern method of handling a severe case of hyperthyroidism typifies the surgical conscience. Here success cannot be cheaply achieved as in abdominal surgery, but the utmost care must be observed in every step of the treatment. Knowledge, skill and a keen conscience are the only guarantors of success. The boldest and most unscrupulous surgeon, the surgeon who would not hesitate to undertake the most difficult abdominal operation hesitates in the presence of such a case. Why? Because he knows that no slap dash methods will avail here. The most painstaking examinations must precede all thought of surgery: repeated laboratory tests, careful blood pressure readings, long

and tedious preoperative preparation, operative procedures planned and executed with the most meticulous attention to detail and the most careful selection of anesthetics. The fear of injury to the laryngeal nerves and parathyroids, the danger of postoperative reactions, the possibility of poor cosmetic results, all of these considerations haunt the careless and inexperienced operator and deter him from hasty and ill advised surgery. Even the remunerative factor is uncertain, for several operations, uncertain results and long delay preclude the expectation of large fees promptly paid. This is the type of surgery that tests the true character and skill of the surgeon. The attitude of mind requisite to success in this field of surgery should be the standard toward which all true surgeons should strive.

In the domain of surgical technic there is need of greater gentleness in handling the tissues and of more paintaking care in eliminating every factor contributing to shock. The use of powerful mechanical retractors, the neglect of hemostasis, the unnecessary bruising of organs and traction on them are all too common. There is need of developing an atraumatic conscience analogous to the aseptic conscience. The true surgeon should shrink from needless trauma as he would from the conscious introduction of infection.

The startling statistics presented by Dr. A. Murat Willis of Richmond at the 1925 session of the American College of Surgeons are convincing evidence that surgical judgment and technic, outside of the great clinics, are still very defective. He showed that in the area of vital statistics the deaths from appendicitis per hundred thousand of population have increased 31 per cent between the years of 1905 and 1922. During the same period there has been a percentage increase of 77 per cent in deaths from gallbladder disease and of 250 per cent in goiter. He did not state that this percentage in deaths from these common affections was entirely the fault of poor surgery, but as these diseases are now treated largely by surgeons it is probable that the rapidly mounting mortality is in large measure the result of injudicious and unskilful surgery. The recommendation of Dr. Willis that a careful survey be made to determine the factors responsible for this increased mortality should have the support of all conscientious surgeons. We as surgeons have flattered ourselves that the treatment of appendicitis was standardized and most of us have thought that the mortality was declining. These facts should awaken us to a new sense of responsibility.

Finally, I wish to discuss the surgical conscience in relation to the fee. I realize that here I am treading on dangerous ground and that I may lay myself open to criticism, but I believe it is incumbent on those of us who are looked on as leaders in the profession to sound a note of warning on this phase of surgical conduct. The division of fees has come to be recognized by all reputable surgeons as a dishonorable and

degrading practice. The American College of Surgeons has done much toward bringing this practice into disrepute. Nevertheless, it is still continued by a large group of surgeons and is defended by some men as justifiable. I believe that any unprejudiced mind will condem it as demoralizing to both the physician who receives a commission for referring the case and to the surgeon who divides his fee. It converts a professional relationship into a commercial transaction and stultifies the conscience of both parties to it. Moreover, it makes a pawn of the patient and tempts both physician and surgeon to recommend unnecessary surgery. While it is still a great evil, it has been driven into the byways and alleys where the scavengers and highwaymen of medicine lurk.

I believe a greater evil than fee splitting is threatening our profession and this is the practice of charging exorbitant fees. There is a strong tendency toward commercialism among surgeons today and the humanitarian and ethical ideals which have been the glory of our profession are in danger of being submerged. Fees out of all proportion to the service rendered and to the ability of the patient to pay are being charged by surgeons of little training and ability. Indeed, much of the surgery for which these exorbitant fees are charged is poorly advised or unnecessary. Many surgeons of standing and ability, indifferent to every sentiment of fairness and generosity, are exacting fees that savor of rank commercialism. Young men entering surgery are no longer willing to do the drudgery and serve the hard apprenticeship that most of the surgeons of this generation experienced. They expect and demand the same fees as men who have earned their reputations by long and arduous efforts. Few of the younger men are willing to enter general practice and for moderate compensation act as the family adviser in matters of health. The vast majority of our well equipped medical graduates are ambitious to enter the surgical specialties soon after graduation and few of them acquire the broad background which five or ten years of general practice will give. The result of this attitude of mind is that people of moderate means can no longer find competent graduates of regular medicine who are willing to advise them and treat their minor ailments for moderate fees. It is necessary now to consult a series of specialists and incur large bills in order to obtain satisfactory medical service. The growth of cults, free dispensaries and lay movements along medical lines can be largely ascribed, I believe, to this failure of the regular medical profession to meet the needs of the average man. I am not decrying the charging of substantial fees when the patient is able to pay and when real service has been rendered, but the present tendency to emphasize the money making side of our profession should be strongly condemned. When the fee becomes the dominant factor in the practice of medicine and when young men come to regard it as

a money making calling, it has fallen from its high estate and we can no longer boast of the nobleness and sacredness of our calling. Osler once said to a group of students entering Johns Hopkins: "If you look forward to a lucrative practice, go home. But if you enter medicine in exactly the same spirit that the missionary leaves for his foreign field, that is, believing that in medicine you best can use your talents for your fellow men, we welcome you." The commercial spirit is not confined to surgery; every branch of medicine has taken its cue from the general surgeon and all are striving to collect fees commensurate with those of the surgeon. The net result is that medical and surgical fees, plus hospital charges, have reached a point where they are prohibitive for any but the rich. To be sure, the increased cost of living, the expensive equipment and appliances essential to the practice of modern scientific medicine have necessitated an increase in medical and surgical fees, but these increased expenses do not justify the exorbitant charges that many surgeons and specialists are demanding.

It would seem that the wave of materialism which has swept the world, and particularly America, since the Great War, has led to an abandonment of many of our professional ideals. In the words of Wordsworth:

> "The world is too much with us: late and soon,
> Getting and spending, we lay waste our powers:
> Little we see in Nature that is ours;
> We have given our hearts away, a sordid boon!"

Surgery because of its spectacular growth in the last twenty-five years, because of its brilliant achievements and its appeal to the popular imagination, has been pecularly liable to abuses and exploitation. While I believe that the vast majority of surgeons are incorruptible and deeply conscious of their great responsibilities, there is a lure for the unscrupulous, the ambitious and conscienceless to prey on the public and profit by the profound confidence in surgery which has been created by conservative, painstaking, unselfish men.

Human life and humanitarian service cannot be measured by the same standards as those that govern the ordinary transactions of life. No sum of money can be weighed against life and health and when a physician strives to justify himself in charging unreasonable fees by comparing them with the price of a beautiful painting, a piece of property or other chattel, he is lowering his own dignity and degrading a noble profession. These matters cannot be adjusted by fee schedules nor by placing charges on a time basis, but by precept and example the high minded men of the profession can set standards of justice and reasonableness beyond which, by common consent, the dignified and honorable physician will not go. We can have no safer guide for our future con-

duct than the torch which has been handed down to us by the master surgeons of this country. What have been their dominating characteristics? They have been first of all men of broad sympathy and deep insight into human nature. They have been men of indomitable will and untiring zeal. They have been men inspired by the vision of a great mission. They have been just, generous and merciful. They have placed human life above every consideration. They have been good citizens, bearing manfully their part in the stress of war. I trust this association will be instrumental in restoring to the surgical profession that spirit of service and that devotion to science and to the welfare of humanity which characterized the lives and teachings of the great masters of surgery.

THE MECHANISM OF ACUTE BACTERIAL INFECTION OF A JOINT

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This article will discuss only those cases of acute arthritis (bacterial infection of a joint) which are caused by the ordinary forms of pyogenic bacteria, staphylococci and streptococci. Cases due to infection by tubercle bacilli, syphilitic virus or actinomyces are not included; nor any case originating in any extraordinary pathology such as that associated with thrombo-angiitis obliterans or senile vascular gangrene; nor cases of joint infection complicating the forms of gangrene associated with diabetes mellitus. Cases corresponding to obscure etiologic factors, such as those commonly known as arthritis deformans, metabolic arthritis and gout, are also not included in this article.

The old terminology used in association with the phenomena of bacterial infection and including such terms as sepsis, septicemia, sapremia and pyemia will not be employed here. The reasons for this were given in a previous article and a simplified terminology was suggested. Here only the terms infection, bacteriemia and general blood infection will be employed, with the following definitions:

1. The term infection will be used as a generic one and will include all the phenomena of a bacterial attack on tissue, organ or the entire body. The various kinds of infection will naturally be described in accordance with the tissue, the organ, or the part of the body involved, and in accordance with the organism or organisms encountered; e. g., saprophytic infection of the uterus, staphylococcus infection of the skin or streptococcus infection of the liver. When no other modifying term is employed it is to be assumed that cultivations of the peripheral blood taken during life are sterile. The differentiation commonly made between local and general infection theoretically does not exist and the terminology is one more of convenience than of accuracy. Local infections must necessarily involve some degree of general constitutional reaction and general infections must necessarily find their beginnings in or be associated with a local focus of infection. As far as possible this differentiation will be avoided or made clear in the text whenever it must be used.

2. The term bacteriemia will also be used in a generic sense to indicate any condition in which living bacteria can be cultivated from the peripheral blood during life. The various kinds of bacteriemia will naturally be described in accordance with the organism found, e. g., staphylococcus bacteriemia, streptococcus bacteriemia.

3. The term general blood infection will indicate a subgroup of the generic term bacteriemia and in this article a distinction will be made between the terms bacteriemia and general blood infection on the following basis: The term bacteriemia is meant to imply a condition in which the organisms demonstrable in the circulating blood by the usual cultural methods are derived from a local lesion somewhere in the body; they are usually small in number, and the faculty of destroying the circulating bacteria is more or less retained by the appropriate antibodies of the blood. The term general blood infection is meant to imply a condition in which in addition to the foregoing a multiplication of the bacteria takes place in the circulation and the faculty of destroying the circulating bacteria is more or less lost by the appropriate antibodies of the blood.

Under appropriate circumstances both of these groups of terms will be employed together, e. g., staphylococcus infection of the skin with staphylococcus bacteriemia or general blood infection. The character of the local lesion in the complete development of any individual infection is best described by the use of the terms primary or secondary (metastatic, subsidiary); thus, primary staphylococcus infection of the skin with staphylococcus bacteriemia or primary streptococcus infection of the tonsil with secondary streptococcus infection of the appendix. The absence of any descriptive bacteriemia indicates that a cultivation of the peripheral blood made during the course of the illness remained sterile.

Acute bacterial infection of a joint finds its origin in many widely differing etiologic factors. In a general way the cases tend to conform themselves into the following groups: (1) those associated with extrinsic causes; (2) those in which the arthritis results from a lesion in its immediate environment, usually by the spreading of a focus of infection; (3) those occurring during the course of a temporary or permanent bacteriemia and in which the joint lesions form metastatic foci.

GROUP 1

A. In civil life bacterial infection of a joint can follow penetrating wounds of all kinds, stab wounds, gunshot wounds, etc. As a general rule these forms of joint infection, if promptly and properly cared for, become restricted to the area of tissue destroyed or in and to the path of the penetrating object, and the results of the injury and the subsequent area of infection are at a minimum when compared with the injury. When neglected or when efficient treatment is not promptly possible, the most extensive process can develop, even to subsequent complete disorganization of the joint and a complete loss of function.

Military wounds follow penetration by missiles of all kinds. These injuries follow along lines similar to those in civil life. The intensity of the infection is usually much more marked, and when combined with the lowered resistances produced by the hardships of modern war-

fare and with the uncertainties and vicissitudes of efficient medical aid under military conditions a greater proportion of cases result in which the excellence of the final result does not approach the ideal looked for in civil practice.

B. Infections of a joint follow compound fractures extending into the articular surface or compound dislocations. In military wounds the track of a missile need not necessarily lie through the joint; in its passage through the bone the resulting comminution is frequently amply sufficient to create an opening into the joint. The end-result depends primarily on the promptness and efficiency of the first aid treatment, and on the extent of actual destruction of the various tissues going into the formation of the joint. Except when the wounds are thoroughly ground with dirt, mud or grease, the amount of permanent infection is relatively small, even though the original contamination is relatively large.

GROUP 2

A. In instances of acute osteomyelitis, I have frequently observed the focus of infection spreading into a joint. The mechanism of this secondary involvement is a threefold one.

(*a*) In many of the cases the infection travels into the joint through the lymphatic channels. Under such conditions an effusion of serous fluid occurs in the joint, which at first is free from organisms but in which organisms can presently be demonstrated. Actual suppuration follows unless because of efficient treatment or other apparent or obscure cause the original focus begins to retrogress, becomes localized and goes on to cicatrization. Sometimes the joint effusion stops just short of the bacteria carrying stage and after remaining so for a variable time it eventually disappears spontaneously. Small "sympathetic" effusions of this kind quite commonly accompany foci of osteomyelitis which are quite close to a joint.

(*b*) In a focus of infection in the bone near the joint surface, it can happen that the gradual extension of the infection in the cancellous and cortical tissue results in more and more destruction of bone until a tract forms leading into the interior of the joint. I have been able to demonstrate this lesion several times during the course of an operation. The clinical course suggests that in some of the cases the bone lesion is a relatively minor one and had, perhaps, preexisted for some time, and that an acute rupture takes place into the joint with the sudden development of high fever, with or without chills, and other signs of an acute infection of severe grade. Positive blood cultures are common under such conditions. Commonly the bone lesion is not recognizable in the clinical picture; the athritis is dominant. In other cases the development of the bone fistula into the joint is a gradual one and is not accompanied by signs of an acute new lesion, or of the exacerbation of a previously existing one; frequently, indeed, the arthritis is seen to develop slowly

during the course of the postoperative dressings on an osteomyelitis wound nearby. In some of these cases it is possible to demonstrate at operation that the bone tissue intervening between the joint surface and the bone focus is carious, by the ease with which an ordinary probe can pass through it and by the macroscopic and microscopic appearances of the tissue.

(*c*) Abscesses in the soft parts resulting from an acute epiphysitis or an acute osteomyelitis also can convey their infection through the lymphatics and so involve the joint. During the course of an operation I have, on several occasions, been able to pass a probe from an extra-articular abscess directly into a joint. As will be pointed out later, perforation of a suppurating joint also can occur and the end-result would be indistinguishable from a lesion resulting from the perforation of an external abscess into the joint. However, in my experience, several of these were distinctly subperiosteal types of abscesses and for that reason I am of the opinion that the direction of the perforating process was inward into the joint.

I have also seen sympathetic effusions in joints which were contiguous with soft tissue abscesses and which were entirely unrelated to any infection in the bone. It has sometimes been difficult to make sure that a pyarthrosis did not exist, but, invariably, proper incision and drainage of the extra-articular focus of infection has been immediately followed by the retrogression of the joint effusion.

REPORT OF CASES

CASE 1.—A young child developed a focus of infection in the general neighborhood of the right knee, with complete loss of function in the joint. It was difficult to decide whether the infectious process had involved the knee. Incision demonstrated an extra-articular abscess leading from the epiphyseal line and the latter was readily demonstrated in the bottom of the wound. There was an uneventful convalescence and healing with no further progression of the focus of infection and with total restoration of function.

CASE 2.—A patient died with the clinical picture of a general blood infection in which a local focus was present in the neighborhood of one knee. Aspiration of the joint yielded a straw colored fluid which was bacteriologically sterile. Necropsy showed a focus in the lower end of the femur and a joint effusion. This was a "sympathetic" effusion.

CASE 3.—In a young child an amputation of the lower extremity was done through the middle of the thigh for an osteomyelitis of the lower end of the femur with symptoms of general infection. The specimen showed a previously done osteotomy at the outer side of the femur; the soft parts were inflamed and somewhat gangrenous; the bone cavity was ragged but apparently in fair condition.

The knee joint was relaxed. The synovial membrane was red and inflamed and had the appearance of unhealthy granulation tissue. The cartilage was not

eroded, but there were inequalities in places especially toward the condyles. There was no fluid in the joint. The crucial ligaments were covered with similar unhealthy synovial membrane and were soft and relaxed. In the notch, the bone tissue was bad, this corresponding to the under side of the femur. The operative cavity in the femur extended to within one-eighth inch (0.3 cm.) of the joint surface; the intervening bone tissue was diseased and carious, but there was no gross perforation. The epiphyseal cartilage had for the most part disappeared.

The accompanying drawings of the various roentgenograms that were taken at intervals demonstrate the development of the arthritis (Fig. 1, *A*, *B* and *C*).

CASE 4.—In 1898 a man developed an osteomyelitis of the femur. Following operation, healing took place and became permanent and there were no recurrences for the next twenty-three years.

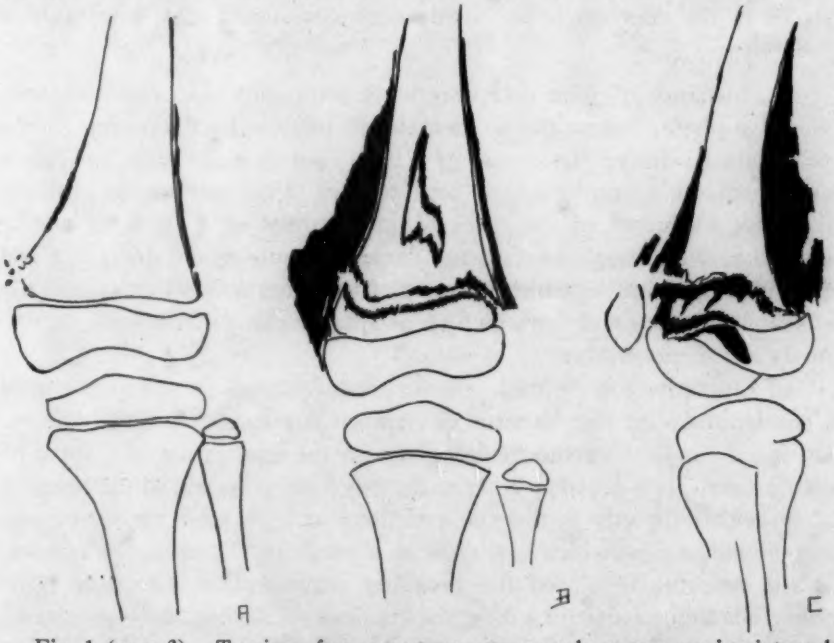

Fig. 1 (case 3).—Tracings from roentgenograms made at progressive intervals of the development of the focus of infection; the figures illustrate the paucity of roentgen-ray evidence of the extent of the final lesion, the method by which the joint becomes involved, and the final degree of destruction.

In 1921 there was a sudden exacerbation of symptoms referable to the site of the previous operation and especially to the knee. At operation suppuration was found in the medullary cavity; the latter was opened to its full extent; the knee joint was not disturbed.

Following this, an abscess developed in the quadriceps bursa from which a thin yellow fluid containing *Staphylococcus aureus* was obtained. Abscesses developed later in the thigh and in the calf of the leg. All of these were properly incised but without getting to the bottom of the trouble. Finally, the whole focus of infection was exposed and it was demonstrated that a sinus existed through carious bone and leading down into the knee joint. The whole outer side of the lower end of the femur was involved in the process as well

as the upper end of the tibia; the joint was thoroughly disorganized. The disease was eradicated as completely as possible and the resulting wound was packed wide open.

Even this was not followed by an arrest of the symptoms and it appeared as if an amputation would be necessary. As a last resort a Mayo arthrotomy was done, and was followed up by a resection of the joint. Thereafter control of the process was obtained and, eventually, healing took place with the development of a stiff knee.

Undoubtedly in this particular instance, the acute exacerbation of symptoms was due to a slow progression of the original bone process and to a relatively acute perforation into the joint.

CASE 5.—An osteomyelitis of the radius was eventfully followed by involvement of the joints at either end of the bone. The course of affairs is amply shown in the drawings of the roentgenographic studies that were made at intervals.

B. Instances of joint infection, more commonly than one ordinarily would suppose, follow the accidental and unintentional opening of the joint capsule during the course of a bone operation for such conditions as osteomyelitis, epiphysitis or bone tumor. This mechanism probably accounts for many of the cases of involvement of a joint which are seen to develop after operation and during the subsequent dressings, and for much of the fever which in many of the cases follows an apparently efficient operation and for which an adequate cause is frequently temporarily not demonstrable.

C. Operative intervention is sometimes followed by involvement of a contiguous joint in which the mechanism is an entirely different one. During the radical osteotomy necessary for the eradication of a focus of osteomyelitis, it is possible either to destroy a large branch of the nutrient artery either directly in the manipulations or by a later spread of any thrombotic process which is present as a result of the operative trauma. When opportunely placed the resulting sequestration may take place either wholly or partially within the confines of a joint; involvement of the latter naturally occurs immediately. The notes of the following case illustrate this possibility very accurately.

CASE 6.—A man entered the hospital with a chronic osteomyelitis of one femur, with fistula formation. At the radical osteotomy that was done, it was necessary to go up into the greater trochanter and somewhat into the neck of the bone in order adequately to remove the diseased tissue. After the operation the patient developed great pain in the hip which persisted for several months before it subsided. The course of events is well shown in the drawings of the roentgenograms which were taken at intervals and which are reproduced here. These show that a large sequestrum had formed and separated out of the bone, which included a large part of the neck of the femur; an arthritis developed coincidentally which lead to a disorganization of the joint, to a subluxation and eventually to a fixation of the femoral head in an abnormal position. It is not possible to explain this arthritis except on the basis outlined in the text of this article (Figs. 2 and 3).

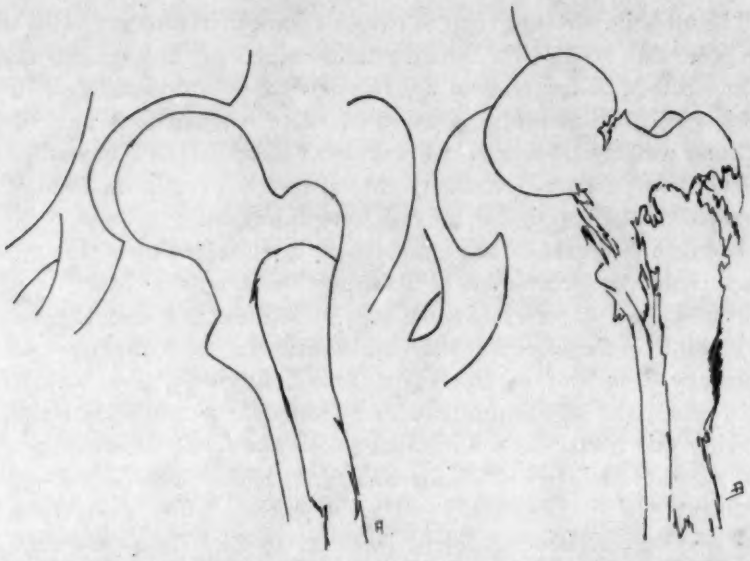

Fig. 2 (case 4).—Tracings of roentgenogram: *A*, extent of osteotomy; *B*, some time later, beginnings of the separation of the sequestrum, coincident with which the hip joint was involved in the focus of infection.

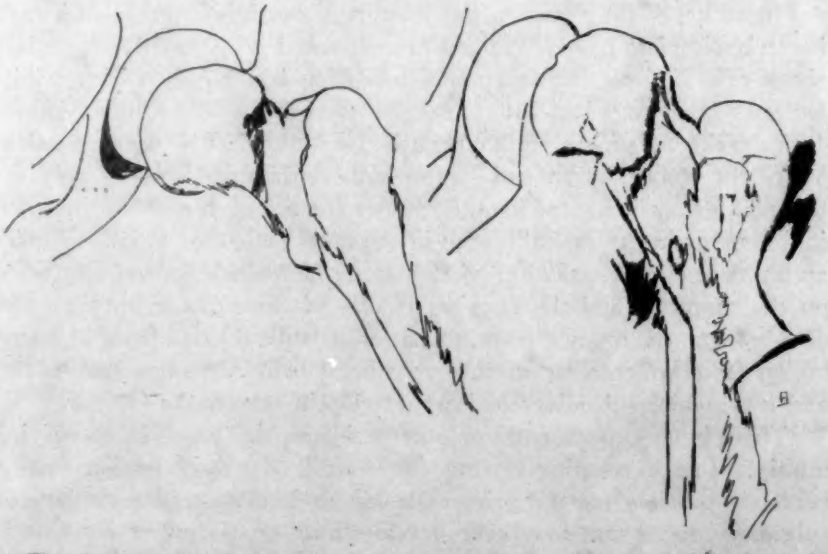

Fig. 3 (case 4).—Later stages in development of focus of infection; the extent of pathologic change is considerable, *B*, showing the complete disorganization of the joint.

GROUP 3

The most important group of cases of joint infection are those which take place as a result of a hematogenous infection. In previous articles the mechanism of bacteriemia was discussed as it forms the most important single cause in the production of acute osteomyelitis in civil life. A similar mechanism takes place with joint infections of a hematogenous origin. For purposes of clarity the essentials of this mechanism are reiterated as they apply to cases of joint infection.

The ordinary case of acute metastatic bacterial arthritis results from a bacteriemia or general blood infection, the origin of which is in the greatest number of cases obscure. In these cases it is thought that the entry point of the infection must necessarily be some surface (skin or alimentary canal) of the body; in actual practice it is assumed that, with few exceptions (genito-urinary infections, furuncular infections of the skin) this surface is the mucous membrane lining of the alimentary canal at points where collections of lymphadenoid tissue are especially prominent (tonsils, especially; Peyer's patches, etc.). At the latter areas a lesion need not necessarily be demonstrable. In a small minority the bacteriemia or general blood infection accompanies or follows a definite entity such as a pneumonia; or a definite focus of infection is present somewhere in the body—a phlebitis, a postpartum sepsis, a furunculosis—to which the bacteriemia or general blood infection is subsidiary and through which in turn the arthritis originates.

In any case the focus in the joint is a fixation point to which the bacteria circulating in the blood are attracted. Commonly there is a single one of these fixation points following which only a single joint becomes involved. But just as often there are more than one of these foci developing either simultaneously or subsequently to each other. When the number of subsidiary foci is more than one some of the fixation points may be located in other tissues and structures, as, for instance, in a bone or in the fascial planes in the musculature of a limb. Under appropriate circumstances previously described which depend altogether on the character and the physical results of the inflammatory process developing at the fixation point, the latter, in turn, forms a point of distribution from which a bacteremia or general blood infection may occur, and from which subsidiary foci can develop in exactly the same way.

There is no experimental or other evidence that helps in classifying multiple foci developing during the course of any infection. It is perfectly possible for the primary lesion to father every secondary or subsidiary focus that may ever develop, and, on the other hand, it is just as possible for any secondary focus to, in turn, form a point of distribution.

The bacteriemia through which joint infections become established and develop are not always demonstrable. It is well known that these

states may be of temporary duration and the presence of bacteria in the circulating blood even for a short period is sufficient to infect any local area. It is thought that temporary states of bacteriemia are constantly occurring even in conditions of health, and that the natural forces of the body are amply sufficient to overcome these so promptly that no evidence of them is perceptible in any way. It is also known that during the dressing of any wound, more so, perhaps, with a wound of bone, bacteria may be pushed into the circulation so that a temporary bacteriemia is present; this ordinarily lasts only a few hours, is occasionally demonstrable, and has no clinical signs or demonstrable effects.

While in extraordinary circumstances bacteria can pass through a surface of the body (the tonsils, for instance) and multiply in the blood, the available knowledge seems to show that ordinarily bacteria circulating in the blood depend for their existence there primarily on the presence of an infected thrombus. The course of events is one of two: 1. Microscopic pieces of the thrombus carrying a number of living organisms break off and circulate through the blood stream until they are disposed of in some way. Sometimes isolated organisms growing on the surface of the thrombus or groups of them in the forms of bacterial emboli are cast off into the blood stream without any particle of the thrombus itself coming away. Clinically, this is a bacteriemia, as previously defined. Fortunately, in most of these instances the natural antibodies destroy the organisms as fast as they are discharged into the circulation and no subsequent effect is noted. In the minority an infected embolus caught into the capillary network of some tissue and held there becomes a fixation point and furnishes the initial stage of a focus of infection. The fact that fragments of the original embolus, after it has been arrested in bone tissue, or of its secondary thrombus thereafter may, in turn, break off and circulate in the blood furnishes the physical basis for the occurrence of secondary points of distribution. This explains the statements made in the previous paragraphs. 2. In addition to the preceding, the virulence of the bacteria may be sufficient to enable them to multiply in the blood stream.

The physical characteristics of the infected thrombus-embolus formation (fixation point) and its resultant effects on the tissues, bone, cartilage capsule, etc., entering into the structure of a joint and the multiplication of bacteria in the blood stream have direct effects on the clinical picture as regards the association of a bacteriemia.

It is necessary to appreciate the fact that in many of the cases of joint infection, an osteomyelitis of greater or less grade is also present; many times the latter holds the dominating part in the clinical and pathologic anatomic picture. Doubtless many of the facts and phenomena of infection, as related to an arthritis, previously and to be presently discussed, especially those related to the demonstrable presence of bacteria

in the circulation, are many times due to a coincidence of the osteomyelitis.

In actual practice it is found that cases of bacterial infection of a joint can be of three clinical varieties:

1. In the first variety a focus is present in one of the joints with well marked local signs and symptoms but without any clinical signs of a general blood infection. A bacteriemia is not present. The physical basis for this variety lies (*a*) in a primary and temporary bacteriemia; (*b*) in the development of a fixation point in a joint, and (*c*) in the subsequent spontaneous disappearance of the bacteriemia.

2. In the second variety, a well marked focus is present in one of the joints with abundent local signs and symptoms and, in addition, there are clinical indications of a bacteriemia as evidenced by the general signs and symptoms and by the demonstration of living bacteria in the blood stream. The physical basis for this variety is the presence of an infected thrombus-embolus formation which serves to keep up a demonstrable bacteriemia by constantly feeding into the blood stream a comparatively small number of viable organisms. Most commonly, after efficient surgical treatment, the bacteriemia eventually disappears and a recovery is made. It must be remembered that any of these cases may at any time pass into the third group.

3. The clinical picture of the cases in this group is that of a profound general infection: there is a marked toxemia. A local joint focus is either not demonstrable at all because of the paucity of local signs and symptoms, or because the latter are hidden in the profound intoxication; or, if present, the local lesion is easily recognized as being of no consequence in the total clinical picture. The physical basis for the clinical picture lies in an extreme and severe general blood infection with highly virulent organisms in which the bacteria are rapidly multiplying in the blood stream and because of which the subject is rapidly being overwhelmed by a tremendous intoxication. The presence of the infected thrombus-embolus formation forms a negligible factor and the few organisms that are derived from this source play only a primary and inciting part in the production of the baceriemia; the subsequent multiplication in the blood stream depends on other factors, the most important of which lie in the high virulence of the infecting organism and in the poor resistance of the subject. An endocarditis is usually found under these conditions. In this variety the local point of fixation plays no rôle in the production of any part of the clinical picture. Usually the pathologic anatomic picture is not in an advanced stage at the time the lesion is exposed, either on the operating table, or, as more commonly happens, in the necropsy room.

In actual disease it seems certain that the cases differentiated in these groups each form progressive stages from the next preceding group. A

case in group 1 may pass into group 2; and, conversely, a case in group 2, having been appropriately treated, may retrogress into group 1 as it proceeds to healing and recovery. These interchanges are constantly occurring in clinical surgery. A case in group 2 may pass into group 3, as previously noted; usually under such conditions there is a continued progression until the eventual fatality. In actual practice cases in group 3 must necessarily first pass through the stages indicated by groups 1 and 2; the time interval may be so short, however, owing to the virulence of the infecting organism, or the relative nonresistance of the subject, as to make these stages unrecognizable. One can explain the cases that apparently begin with the characteristics of the cases in group 3 in this way. In many cases characteristics can be distinguished which belong to both group 2 and group 3, and so far as any case partakes of characteristics not belonging to its group, it differs in its clinical manifestations. I have never seen a case in group 3 retrogress spontaneously into group 2; it seems almost impossible to believe that such retrogression can ever occur. It is often a matter of great difficulty, clinically, to make correct judgments as to the coincidence or the absence of an osteomyelitis with an acute joint infection, as to the relative dominance of the one over the other part of the total clinical picture and as to the relation of either of them to an accompanying bacteriemia. This is an especially great difficulty in the most severe cases of group 3, even though in these cases a fatality is always to be expected and the differentiation would, therefore, be of no practical moment.

In the milder cases, much depends on a judgment of this kind as far as operative indication is concerned; for in the acute joint infections with osteomyelitis and positive blood cultures, it is essential to clear out the bone focus immediately, while in pure joint infections with positive blood cultures and no bone involvement a more conservative policy is many times permissible and perhaps even advisable. Bacteriologic studies are frequently of help here; if *Staphylococcus aureus* is demonstrated in the peripheral blood, the chances are much more in favor of an osteomyelitis also being present and the mere demonstration of the organism is frequently an indication for operation. In the presence of streptococci or pneumococci, the chances of bone involvement are at a minimum and operation is usually deferred or not done at all as no bone involvement is expected under these conditions.

In actual disease the occurrence and position of secondary or subsidiary foci (fixation points) depend a great deal on the physical characteristics of the blood vessel network of the individual structure or organ involved. In joint disease this must necessarily include the blood vessel network of the bone and cartilage entering into the joint structure as well as that of the joint capsule and the synovial membrane.

A typical specimen of the circulation in a long bone is shown in figure 2, *A*. There is a separate circulation for the diaphysis and for the epiphysis. The circulation of the epiphysis enters most often at more than one point, though often a main channel can be distinguished. The circulation of the diaphysis is derived from a large vessel, the nutrient artery of the bone which enters a little to one side of the center of the shaft. Immediately, the main vessel divides into a number of large branches which pass, some of them upward and some of them downward toward either end of the shaft. A diffuse network is formed which supplies the entire interior of the bone and its medullary cavity. Toward the end some of the main branches become end vessels. There is a free anastomosis between the plexus of vessels thus established and the vessels derived from the periosteum through Sharpey's fibers. In a growing bone, with the epiphyseal cartilage still present, there is little direct anastomosis between epiphysis and diaphysis and a relative avascular area results; in a fully grown bone there is an extensive anastomosis between the two.

The blood supply of joints in general is not subversive of any classification. The blood supply is derived from a variable number of large vessels in an irregular manner. It then enters the joint by a number of derivative vessels and after perforating the capsule at various places divides and supplies the joint interior. There is a minimum of blood supply in the synovial membrane and practically none in the cartilaginous tissue; both these elements derive a great deal of their food supply through the lymphatic circulation.

A fixation point is formed by the arresting of an embolus (or by a thrombus formation) at some point of this vascular network either in the bone or other joint structures. The actual point depends more on chance than on anything else and is decided by the physics of the local bone or joint circulation at the given moment. Various pathologic pictures result, depending on the size of the plugged vessel, the relative position of the plug, the powers of vascular anastomosis, etc., in conjunction with the character and virulence of the bacteria giving rise to the infection. The dominant characteristics of the pathologic pictures are: (1) a thrombo-arteritis or thrombophlebitis, and (2), in the cases with osteomyelitis, a necrosis of bone and cartilage cells consequent to the disturbance of circulation. The physical characteristics of the pathologic picture depend to the largest extent on the second factor.

The peculiarities of the local capillary circulation at the given point determine whether the confines of the metastatic focus of infection shall be limited entirely to bone or entirely to the joint or whether a simultaneous involvement of both bone and joint shall take place. The anatomic possibilities find their examples commonly in clinical practice and can be grouped as follows:

1. When the fixation point for the thrombus-embolus formation is somewhere in the confines of the soft structures of the joint, the resulting pathologic process is limited to the interior of the joint and passes through the stage of a serous sinovitis to that of a frank suppuration. If regression begins at this point, either spontaneously or after surgical incision, the end-result may be perfect or one approaching the ideal. Should, however, the progress continue or the infection spread to or originate in other structures of the joint, especially bone and cartilage, there must necessarily be structural change in the joint and a corresponding eventual interference or abnormality in its anatomy and physiology.

Fig. 4.—Scheme of blood supply of typical long bone obtained by injection with a medium opaque to the roentgen ray (from "Untersuchungen über Knochenarterien" by E. Lexer, Kuliga and Türk).

Simple joint infection of this kind is most apt to occur when the inciting organism is the pneumococcus or a closely related strain of the streptococcus group. The notes of the following case serve as an illustration:

Case 7 (Alexander).—Ten days before admission to the hospital the patient developed a pharyngitis. This was followed by indefinite wandering pains in a number of the joints, and there was irregular fever of a more or less intermittent type. Finally pain developed in the right ankle, became aggravated and persisted, and there was fever ranging to 104 F. The tissues around the ankle became reddened and tender and there was total loss of function. Incision demonstrated a thick greenish pus in the ankle joint and the neighboring joints of the tarsus. Pneumococcus I was cultivated from the pus.

There was an uneventful convalescence following incision. No evidence was present to make one suspect bone involvement. At the time of discharge from the hospital full function had been regained.

2. In children (and young adults) the fixation point is commonly in an epiphyseal line. A number of possibilities result, depending on the relation of the epiphyseal line to the interior of the joint capsule and to the line of reflection of the synovial membrane. Anatomically, the epiphyseal line has a variable relation to the joint interior, depending on the physical structure of the individual joint: in some of the joints the line lies altogether outside the joint; in others it lies outside the joint only partially; in still others it lies altogether within the joint. The observable clinical possibilities are as follows:

A. An epiphysitis develops with or without abscess formation, and during the entire course of the infection there is no demonstrable evidence pointing to involvement of the joint. The physical basis for this naturally lies in the location of the fixation point in an epiphyseal line which is entirely outside the joint.

B. An epiphysitis develops with or without abscess formation and the clinical signs of joint involvement come only later. If this should appear before any operative incision, it indicates that the fixation point was originally situated in a part of an epiphyseal line which was outside the joint and that joint involvement took place, because of the spread of the infection along the epiphyseal line into a portion of it which lay within the joint or because secondary sequestration opened a path into the joint. If the signs of joint involvement come after incision, the possibility is always present that the latter was due to the operative intervention, either accidentally or, perhaps, purposefully.

C. An acute joint infection develops and at operation it is possible to demonstrate a focus of infection in an epiphyseal line in the interior of the joint. It is immaterial whether the given epiphyseal line lies wholly or partially within the joint; the focus of infection is in that part of it which lies within the joint.

3. The anatomy of the interior bone circulation has been discussed exhaustively elsewhere and has been referred to previously in this article. The mechanism of infection limited to the bone was also discussed fully at that time and needs no repetition. Suffice to say here that the fixation point in the vascular network of the bone may be so situated that the focus of infection resulting therefrom may lie at least partially within the interior of the joint. An arthritis coexists from the beginning. In children this, of course, includes the commonly seen epiphyseal infections.

4. It is, of course, perfectly possible for both bone and joint to be simultaneously involved because of the formation of more than one fixation point. I am convinced that this is a common occurrence.

In actual disease the position of fixation points is probably determined by some kind of local trauma at the given point. This has been referred to on a previous occasion. I include under the general term of trauma all varieties, mechanical and physical trauma, chemical trauma. In clinical experience the cases group themselves into (*a*) those in which there is a distinct history of a definite physical trauma and (*b*) those in which no such history is elicitable.

A. Cases in which the trauma is a distinct physical entity are, of course, common. I give the notes of one case in which the sequence of events is suggestive.

CASE 8.—A man sustained a fracture of the olecranon process of the ulna. The healing was marked by marked disability and by a later development of fever. Eventually this was proved to be due to a suppurative arthritis of the elbow. It is probable that the joint infection took place through the medium of the fractured bone.

This is an extreme case of trauma. There are many other cases in which the degree of the trauma and its extent varies all the way down to minor grades and until it is so slight as to be barely, or not, recognizable.

The physical basis for this consists of a hematogenous infection in a gross or microscopic hematoma associated with blocking of the circulation at one or more points because of the tearing of the vessels: this is a fixation point for any bacteria carried in the blood stream.

There are other cases in which trauma occurs accidentally during the course of a well established bacteriemia. In cases of general infection the mildest trauma is almost certain to be followed by local infection. In many cases the trauma is so slight as not to be recognized.

B. This group includes all the cases in which there is no history of trauma. Undoubtedly in some, at least, of the cases in this group, trauma was present but passed unnoticed, most probably because of its slight degree or because of some other undiscoverable cause.

It is possible that in some of these cases a certain form of negative or passive trauma is produced by a temporary disturbance of the capillary circulation in a circumscribed area leading to a temporary localized anemia. This might conceivably be produced by a fragment of blood clot, which, having become dislodged at some other distant point, becomes caught in the capillary network of some joint structure. Necessarily the embolus need not carry bacteria, but, once having become arrested in its circulation, it furnishes an ideal environment for the attraction organisms circulating in the blood.

Circulatory changes which cause changes in nutrition are the physical basis for the "chemical traumas" that I previously mentioned. Many cases with no definite etiologic history of trauma undoubtedly have this form of trauma as a contributing cause.

From what has been said heretofore, it must be apparent that in any given case the presence of a bacteriemia can be referred (1) to the primary lesion; (2) to its secondary focus in the joint; (3) to the presence of another subsidiary focus (bone or other) which by itself is capable of creating a bacteriemia; (4) to the presence of a bacterial valvular lesion, and (5) to the presence of some unrelated complication capable itself of giving rise to a bacteriemia or general blood infection. In any given case it is always important to be able to classify properly the bacteriemia demonstrable. The clinical possibilities are the following:

1. In many of the cases a focus of infection is demonstrable in only one joint. In most of the cases in this group the comparatively small number of bacteria demonstrable in the blood circulation (plate culture method) indicates that the bacteriemia results from the demonstrable local lesion. If, following an adequate operation, the blood becomes sterile, it can properly be assumed that the bacteriemia had resulted from the joint infection. If the bacteriemia does not disappear following the adequate drainage of the joint, the presence of an associated bone infection must be assumed. The presumption is stronger if the inciting organism of the joint infection is proved to be a staphylococcus. Exploration of the contiguous bone is then indicated. In the averge joint it sometimes becomes a matter of difficulty to locate the bone focus, or to decide which of the bones entering into the joint structure is to be explored, although commonly the presence of localized tenderness is an efficient guide. Should a competent focus be found and removed surgically and should this be followed by a disappearance of the bacteriemia, it can again be properly assumed that the latter resulted from the focus of osteomyelitis. When the bacteriemia still persists and the surgeon is certain that the bone lesion has been so thoroughly removed as to be apparently impossible of causing the bacteriemia and when the appearances of the bone wound corroborates this impression, the bacteriemia should be used as an indication that some other focus exists which must be found and removed in order to render the blood sterile. Many times this proves to be the case; but when it does not, the original focus of osteomyelitis should be examined again and revised operatively. If the bacteriemia still persist and the number of demonstrable bacteria is still comparatively small, an explanation of the bacteriemia becomes impossible for the moment, although it must necessarily be assumed that some other focus does exist which is causing the blood infection, and which for the moment is not demonstrable. Undoubtedly in some cases an obscure primary lesion exists which serves to keep up the bacteriemia. Fortunately, in most of such cases the natural forces of the body are ample after a sufficient elapse of time to render the blood sterile. A bacterial endocarditis must be excluded in all such cases.

If the inciting bacterium of the joint infection is a streptococcus and the patient is in the appropriate age, an epiphysitis is to be looked for; doubtless the operating surgeon will have demonstrated this lesion in exploring the joint and in establishing competent drainage. In order to conserve the normal growth of the bone at the given epiphyseal line, total or partial removal of the epiphyseal lesion is not advised and it is better surgery to allow nature to sequestrate that which has already been destroyed by the infection. Under these conditions, the bacteriemia will persist; usually, however, the natural protective forces of the body are sufficient eventually to render the blood sterile. If the grade of the bacteriemia should, however, increase to the dangerous point, further radical surgical measures become imperative.

In the presence of a pneumococcus infection, it is most exceptional for bone involvement to be present. Bacteriemias are not common, and are usually due to another lesion in the body at a distance from the joint infection. Conservative treatment of the joint is indicated.

2. When foci of infection coexist in more than one joint in the presence of a bacteriemia, the explanation of the latter becomes a matter of exclusion. Similar rules to those outlined in the last paragraph apply.

3. In a few of the cases, comparatively speaking, the primary lesion is demonstrable as well as one or more subsidiary lesions. In the majority of the cases, the primary bacteriemia disappears after efficient surgical treatment directed toward all the demonstrable lesions. In a few cases, however, the bacteriemia persists. Although in some of the latter cases, because of the character of the infecting organism or because of other reasons, it is possible to say with a fair degree of certainty that the primary lesion is keeping up the bacteriemia, in all of the others the proper explanation becomes a matter of exclusion also in accordance with the rules laid down.

4. In some of the cases of joint infection with bacteriemia a complication develops which is apparently unrelated to the arthritis. Except in those cases in which the complicating lesion is known from previous experience to cause a bacteriemia or general blood infection, the proper explanation again becomes a matter of exclusion as previously indicated. In any of these groups it is important to know the relative quantitative degree of the blood infection by an estimation of the number of organisms per cubic centimeter of blood (plate culture method). Then a comparison of any one blood examination either with preceding blood cultures or with subsequent ones readily gives a method of distinguishing whether improvement is or is not occurring.

5. Any of the local conditions indicated in the preceding four groups may be associated with a general blood infection in which the blood cultivations show that large numbers of viable organisms are circulating in the blood. It is to be assumed under such conditions that the bacteria

are multiplying in the blood in addition to whatever else they are doing; the prognosis must therefore be a serious one. The local lesion, or lesions, becomes a matter of least importance. The usual course of affairs includes a steady progression of the general blood infection until a fatality occurs. Exceptionally, improvement occurs and the patients recover. Some patients are admitted to the hospital when the general blood infection has already reached an extreme degree, that is, in a high grade of sepsis; such patients should not be operated on for any of their local lesions as they invariably die within a short time.

Patients in the first four groups of this classification may, at any time, as has been indicated previously, pass into group 5. They then assume characteristics of this group and the clinical manifestations increase in gravity proportionately and absolutely. It is rare for the opposite course to be followed.

In the group of joint infections with and without osteomyelitis and with bacteriemia, the disappearance of viable bacteria from the blood stream, as demonstrated by the blood cultivations, is many times due to the mechanical operative removal of the part of tissue carrying the infected embolus-thrombus formation. In epiphyseal lesions, mechanical removal of the focus of infection is not done; the disappearance of any accompanying bacteriemia must then, necessarily, be accomplished by the natural antibacterial agencies of the body. In others, the disappearance of the bacteriemia is a sudden thing due to the extrusion of the infected clot into the wound surface, or to other nondemonstrable cause of generally similar nature, or to the control of the infection by the relatively strong natural resisting powers of the patient. In still other cases, the bacteriemia becomes a more chronic affair and persists for some time before finally disappearing; anatomically this must be due to a slow healing of the lesion and the isolation of the infected clot by dense scar tissue, or, functionally, by the slow sterilization of the infected environment by the natural forces of the body.

A REVIEW OF UROLOGIC SURGERY

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(Concluded from page 773)

TESTIS AND VAS DEFERENS

Tumors of the Testis.—Keyes [44] states that a high mortality rate accompanies the treatment of malignant tumors of the testis by orchidectomy only. It is emphasized that for more successful treatment earlier diagnosis and more extensive operation or treatment by radiant energy must be made. Five conditions must be considered in the differential diagnosis: syphilis, hematocele, hydrocele, tuberculosis and cryptorchidism. Gibson and Kutzmann in their radical operations found that in only 50 per cent of cases could all malignant nodes be removed. Colley reported seventy-eight cases treated with serum; only twenty-two patients survived more than four years.

Keyes reports a case in which there was marked emaciation, a large testicular tumor, and extensive secondary masses in the abdomen. Orchidectomy was performed one week after treatment with radium packs. The abdominal masses subsided in several weeks, and ten years later the patient was living and well. Dean reported sixty-three cases in which treatment was carried out by radiation of low voltage to the testis and high voltage to the abdomen before orchidectomy. High voltage irradiation was repeated two months after the first treatment, orchidectomy having been performed in the meantime. Twenty-six patients (41 per cent) survived, six were well more than three years, and two more than five years. Thirty-nine cases were termed "recurrent inoperable," the patients having developed inoperable local recurrence or inoperable metastasis. Of these, eight (20 per cent) survived from six months to seven years after the first irradiation, showing that this treat-

44. Keyes, E. L.: Malignant Tumors of the Testicle; Diagnosis, Prognosis and Treatment, Am. J. Roentgenol. **15**:44-49 (Jan.) 1926.

ment has at least arrested the disease. Following irradiation and orchidectomy 20 per cent remained well, in contrast to almost complete failure following simple orchidectomy with irradiation. It is pointed out that comparison is difficult between surgery and radiotherapy, since the latter begins where the former ends.

[ED. NOTE.—The surgical removal of a primary malignant tumor with its metastatic growths is fundamental, depending primarily on an early accurate diagnosis, and also on complete permanent removal of the tumor. Applications of these principles in treating malignant conditions has markedly lowered the mortality rate. Diseases of the mouth, breast, uterus and testis are examples, and the fact that metastasis in these conditions occurs primarily along the draining lymphatics, which are surgically removable, still makes possible a small percentage of cures even in the later stages of the disease. Bloodgood has found, in thirty years' experience, that cancer of the tongue, when treated in the early stages, yields a cure in 62 per cent of cases, while only 12 per cent are relieved in the later stages. Hinman, in his radical operation of removing the lymphatic drainage of the testis, has raised the possibility of cure from 15 to 30 per cent in teratoma testis.

The advent of modern efficient radiotherapy tends to modify treatment somewhat. The encouraging results noted in recurrent inoperable cases are instructive, but should not be nullifying in those cases that can be cured by complete surgical removal. Undoubtedly radiotherapy is the treatment of choice in those cases exhibiting palpable abdominal metastasis. Levin has stated that the highly specific action of radium on the testicular cells undoubtedly explains the remarkable beneficial effect on some malignant tumors of the testis. The rays tend to destroy the spermatogenic elements without apparent injury to other elements. It has accordingly been our experience that the beneficial effect has been only in the seminoma (embryonal carcinoma). This is due to the fact that this type of tumor is derived from the spermatoblasts and is therefore regarded as especially amenable to radiotherapy; the mixed type of tumor (teratoma) is not necessarily so susceptible. It is interesting to note that Chevassu, the originator of the modern radical operation for testicular tumor, uses radiotherapy over the abdomen in the seminoma type of testicular tumor with metastasis and reserves the radical operation for the teratoma or mixed tumor.]

Bell [45] states that the seminoma and teratoma groups constitute the greatest number of tumors of the testis. Seminoma arises from a proliferation of the cells of the seminiferous tubules in the same way that glandular carcinoma arises in other organs. These are usually noticed in the fourth decade and they grow more slowly than the teratoid

45. Bell, F. G.: Tumors of the Testicle: the Spermatocytoma Group, Brit. J. Surg. **13**:282-301 (Oct.) 1925.

carcinoma. They present in the main a specific structure, which may be definitely related to the seminiferous cells but is subject to certain variations. The question occasionally arises as to whether a tumor is carcinomatous or sarcomatous. Carcinomatous features usually prevail, but it is common to find mixed histologic characters in the same tumor. This feature is probably related to the mesothelial origin of the seminal cells and to reversionary tendencies. Like most germinal cell tumors, the seminomas behave like carcinoma and spread by way of the lymphatics. Occasionally, however, spreading by way of the blood stream suggests sarcomatous characteristics.

Vasotomy.—Belfield [46] finds that three possible injuries may take place through vasotomy: (1) injection of the solution outside instead of within the vas; (2) epididymitis, and (3) occlusion of the vas.

Extravasal instead of intravasal injection is possible through either of two errors: failure to distinguish the sheath from the vas or puncture of the vas by the sharp point of a needle after introduction into its lumen. Even the hypodermic steel needle whose point has been filed off may, after introduction, perforate the vas. For this reason Belfield has long used and recommended the blunt silver canaliculus needle.

Epididymitis does not, and probably cannot, result from the mechanical injury or from the effect of ordinary chemical solutions properly injected. Twenty-two years ago, before performing vasotomy on the patient, Belfield carried it out on dogs; when, contrary to his expectation, epididymitis did not occur, he injected mild silver protein solution toward the testis, and found it impossible to make this black liquid pass beyond the tail of the epididymis. In an experimental study Rolnick also proved, and by roentgenograms demonstrated, the impossibility of injecting beyond the tail of the epididymis of the dog. A similar demonstration has been made by Luys of Paris, in his study of vasotomy, and he has adopted this procedure in place of his earlier practice of injecting the vesicles through the ejaculatory ducts. In man he has never seen epididymitis caused by vasotomy. He has, however, seen epididymitis follow a pus infection of the vasotomy wound; this is, so far as he knows, the sole causative relation between vasotomy and epididymitis.

Occlusion of the vas is possible through extensive laceration of the vas, its sheath or adjacent tissues, which is of course needless in performing vasotomy. Occlusion may occur through the injection of chemicals that destroy the epithelium lining the vas, with subsequent union of the denuded surfaces. Of the many solutions used, many are the milder silver protein compounds, mild silver protein and neosilvol, in 10 per cent solution; the recent chlorine preparations, hyclorite, and chlorazene

46. Belfield, W. T.: Injuries Possible Through Vasotomy, J. Urol. **14**:349-353 (Oct.) 1925.

1:200, are not known to destroy the epithelium of the vas. Of the newer mercurial bactericides, mercurochrome-220 soluble in 1 or 2 per cent solution is reported as harmless by some clinicians (Cumming, Ockerblad) although found to be harmful by others (Kile); Rolnick found a 2 or 3 per cent solution destructive to the epithelium of the vas in dogs. Possibly a weaker solution, 1:300 or 1:500, might prove both efficient and harmless.

Occlusion of the vas may be induced by infection of the wound, with subsequent cicatrix formation. An insidious cause of occlusion is the regurgitation, past the vesicle into the wound, of some substance which, while harmless to the lining, provokes in connective tissue a cicatricial formation by which the vas is compressed. Belfield has seen this only through the use of colloidal silver solution. To avert such regurgitation he has compressed the vas by a silkworm stitch, passed through both edges of the skin incision and under the sheath of the vas, leaving it in position for four days.

Thomas [47] differentiates vasopuncture and vasotomy or vasostomy. His technic of vasopuncture is as follows: The seminal vesicles are emptied of their inflammatory products as completely as possible by massage just prior to injection. A vertical incision of about 1 inch (2.5 cm.) is made in the skin and fascial sheaths, and the vas isolated and brought out of the wound on the curved flat end of a probe; or, preferably, the vas is encircled through its sheaths by the towel clips as soon as the skin is incised, facilitating its exposure, or it is cut directly down on. The fascial coverings are then stripped from the vas, which facilitates the introduction of the needle. A few cubic centimeters of sterile water is injected to determine the patency of the vas and ejaculatory ducts. The lost resistance as the needle enters the lumen of the vas, together with the visible ascent of a tiny black column in the axis of the vas after the injection of about 2 drops of colloidal silver, without resistance, inform the experienced operator that the needle is properly in the lumen and that there is no stricture of the vas. If for any reason the needle cannot be correctly introduced into the lumen of the vas, or if a stricture is found, the injection is not attempted, as a disagreeable vasitis, funiculitis and occlusion of the vas may result. In the absence of any mishap or obstruction, the syringe is filled, preferably with 3 to 5 per cent solution of one of the silver protein preparations, or perhaps 0.25 per cent chlorazine, and the quantity slowly injected. As the needle is withdrawn pressure by gauze prevents reflux, and subsequent regurgitation and extravasation into the spermatic cord are prevented by the introduction of a fine plain catgut suture through the external

47. Thomas, B. A.: Vasopuncture, a Technical Modification of Vasotomy for Seminal Vesiculitis, J. Urol. **14**:331-347 (Oct.) 1925.

coat of the vas. Herein rests the superiority of vasopuncture over vasotomy, as the operator is better able to control regurgitation from the vas and its attendant disastrous consequences; in vasotomy such perfect control does not exist, and there is more traumatism and greater proclivity to infection and formation of stricture.

Mark [48] states that whether drainage of infected vesicles is established through the normal point of discharge as provided by nature, or by opening the sac through some other point of selection, must depend on the judgment of the surgeon based on the degree of pathologic change. It is equally as axiomatic that when the infection has invaded the walls of the sac to the degree that drainage will not suffice, and when the removal of the sac is not incompatible with life, such removal is indicated and justifiable if the restoration to health of the patient demands it. Further, it is recognized that the treatment of an infected sac by bactericidal agents without drainage avails nothing and is essentially poor surgery. Mark concludes that vasotomy is indicated only when this operation facilitates or establishes drainage. Horsley has shown that when a foreign substance is introduced into a cavity lined with epithelium, two forces are set at work for its expulsion and protective drainage, spasmodic efforts on the part of the surrounding musculature and a reversal of the lymph stream. He believes that too much stress cannot be laid on these physiologic factors in considering the good effects that may be secured from vasotomy.

Wesson [49] reports a series of forty-seven cases of vasitis; the majority of these cases had been referred to him by insurance men for examination with the statement that operation for hernia had been advised. These cases had been diagnosed because of the history of pain in the groin following a strain, and the presence of bubonocele or thickened tender spermatic cord, which interfered with accurate palpation of the inguinal rings. Urine was found infected in eighteen cases; residual urine, secondary to median bars in four; pus in the prostate and seminal vesicles in forty-seven; tender thickened vas in forty-seven; chronic epididymitis in thirty, and genital tuberculosis in three.

CARCINOMA OF THE PENIS

Dean [50] reports his results in the use of radiotherapy in sixty-one cases of carcinoma of the penis. The following groups are considered: 1. Six cases in which there was a superficial local lesion without metastasis. Five of these patients were living and well from one year to five

48. Mark, E. G.: Indications for Vasotomy, J. Urol. **14**:323-330 (Oct.) 1925.
49. Wesson, M. B.: Industrial Hernia Versus Seminal Vesiculitis and Vasitis, California and West. Med. **24**:212-217 (Feb.) 1926.
50. Dean, A. L., Jr.: The Treatment of Epithelioma of the Penis with Radium and Roentgen Rays, Am. J. Roentgenol. **15**:36-43 (Jan.) 1926.

years and eight months after irradiation. 2. Thirty cases in which there was extensive local tumor without metastasis. Twenty-one of these patients were living and well, seven from three months to one year, three from one year to two years, three from two to three years, two from three to four years, and six from four to five years; five were known to have died, and four were lost from the records. 3. Sixteen cases in which there was extensive local tumor and metastasis to the groin. Four of these patients were living and well from one year to three years and seven months after irradiation; seven were known to have died, and five were lost from the records. 4. Eight cases of postoperative recurrence; three of these patients were known to be living and well from four years to five years and three months later; three were known to have died, and two were lost from the records. 5. One case in which irradiation was carried out postoperatively as a prophylaxis against recurrence. This patient was living three years and two months later; there had been metastatic growth in the groin which was removed at operation.

Dean concludes that in the treatment of primary epithelioma of the penis and metastasis the element of infection must be eliminated as soon as possible; that a superficial epithelioma should undergo complete regression when treated with a surface applicator of radium emanation, 65 millicurie hours for each square centimeter, filtered through 0.5 mm. of silver, and that if the tumor has invaded the cavernous tissues the treatment of choice is thorough irradiation followed by conservative amputation. Surface application of radium emanations is preferred, as it is less traumatizing and more convenient. In some cases inguinal metastasis disappears after irradiation with the roentgen rays. If after such treatment the metastatic nodules do not steadily decrease in size, firmness and degree of fixation, and the cause of delay cannot be ascribed to infection, careful resection is in order. The high voltage roentgen-ray irradiation is more efficient than that delivered by the low voltage machine for the treatment of metastatic nodules of all depths. When high voltage roentgen-ray machines are available it is unnecessary to depend on the radium pack for deep application.

URETHRA

Diverticulum.—According to Verriotis and Defrise,[51] cases of urethral diverticula of congenital origin in women are rare. The most frequent causes of acquired diverticula are trauma during delivery, direct trauma, inflammatory conditions or the opening from inside the urethra of cystic cavities of the urethrovaginal septum. These conditions usually

51. Verriotis, T., and Defrise, A.: Des diverticules urétraux chez la femme, J. d'urol. **21**:97-122 (Feb.) 1926.

suggest disease either of the genital system or of some other portion of the urinary tract. There is usually more or less infection of the diverticular pouch. The diagnosis is definitely determined by urethroscopic or roentgenographic examination. Radical operation gives the best results; it consists in resection of the diverticular pouch and in the urethrovaginal plastic operation. Without surgical treatment the condition rarely improves.

Young and Shaw [52] classify urethral diverticula as congenital and acquired. The latter arise (1) from dilatation of the urethra due to urethral calculus or urethral stricture, and (2) with perforation of the urethra resulting from injuries to the urethra, rupture of abscesses into the urethra, and rupture of cysts into the urethra. A report is given of a case of diverticulum following perineal prostatectomy. The diverticulum was completely excised. The division was made at the connection with the prostatic urethra. The urethral opening was closed with mattress sutures of plain catgut. Sutures were used to tighten the external sphincter. An inverted skin incision was made in the line of the wound made for the old prostatectomy. The sac was easily exposed without opening and followed downward into the depths of the perineum. It was about 1 inch (2.5 cm.) in diameter externally and had a gradually narrowing gourdlike neck, which in its deeper portions was about 5 mm. in diameter externally. The neck of the sac was followed to its juncture with the urethra at the apex of the prostate, where it was excised. The connection was only 2 or 3 mm. in diameter. The mucous membrane was then turned in with a pursestring suture of plain catgut. Examination of muscles in the region of the triangular ligament and external sphincter showed definite impairment. There was no recurrence of the diverticulum after operation; there was moderate incontinence, usually during the day.

Duplication.—Fronstein and Saïgràjeff [53] state that anomalies of the urinary and sexual organs occur frequently on account of the fusion of these organs in embryonic development. In 148 anomalous cases of such type, eight cases of duplication of the urethra were noted. Double urethra, beginning at the external orifice and belonging to the pendulous portion of the urethra, is rare, and a double urethra extending to the bladder is unusual.

Of four cases described by Fronstein and Saïgràjeff, one involved the posterior urethra and the posterior portion of the pars pendula penis. In the first case described there was an accessory urethra, 15 cm. in

52. Young, H. H., and Shaw, E. C.: Urethral Diverticula, South. M. J. **19:** 42-45 (Jan.) 1926.

53. Fronstein, R. M., and Saïgràjeff, M. A.: Zur Frage der Duplikatur der Harnröhre, Ztschr. f. urol. Chir. **17:**187-204, 1925.

length, lying dorsally and extending from the outer opening of the urethra to the prevesical tissues, but no connection with the bladder or the true urethra was noted. A histologic structure similar to the true urethra was noted. Resection was carried out because of infection. A good result was obtained. In a second case two parallel channels occupied the anterior portion of the penile urethra. The dorsal channel connected with the lower one 6 cm. from the meatus. A third patient presented a dorsal blind canal leading 3.5 cm. backward and separated from the lower canal by a thin membrane. The fourth case is remarkable in that none other like it can be found on record. The accessory channel found at necropsy extended from the bladder to the peripheral third of the pendulous portion of the urethra. It contained the openings of the ejaculatory ducts and the colliculus seminalis. It passed through the prostate parallel to the true urethra, which was markedly constricted. Farther forward the accessory channel became dilated and continued to the end of the penis.

The authors review the literature on urethral duplication and seek to show that the condition is caused by embryonic maldevelopment of entoderm and ectoderm of the sinus urogenitalis. When possible radical extirpation of the accessory channel is the treatment recommended.

[Ed. Note.—The urologist, perhaps as frequently as any specialist, is called on to consider anomalous development of the structures with which he deals. To trace the embryogenetic relationships of the parts involved in such malformations affords unusual opportunity for detailed anatomic study, both from the standpoint of understanding the individual anomalous structure and from the more practical point of view as to how best to apply plastic surgery in reconstructing the parts for proper function. In the case of duplication of the urethra the foregoing article is timely, as Fronstein and Saïgràjeff carefully explain the different types encountered, the lesions that are likely to arise in consequence, and the technic for handling the individual case to best advantage.]

Stricture.—Huddy,[54] in a review of the subject of internal urethrotomy, reports the study of 109 operations on 107 patients. The main types of stricture which require urethrotomy are: (1) the narrow type, which is permeable with considerable difficulty and in spite of repeated efforts will not dilate readily; (2) the resilient type, which dilates but as readily contracts, and (3) the type in which perineal fistula is associated, provided the fistula persists solely because of the presence of a stricture in front of it and not on account of a chronic infective condition.

Operation is contraindicated in cases in which the stricture is impermeable. The operation should be preceded by suprapubic drainage of

54. Huddy, G. P. B.: Some Considerations of the Operation of Internal Urethrotomy and the End-Results Thereof, Brit. J. Surg. **13**:458-465 (Jan.) 1926.

the bladder if there is evidence of renal insufficiency or marked urinary infection. A periurethral abscess should first be drained and internal urethrotomy performed when the infection has subsided. Urinary extravasation is best treated by free incision into the infected parts combined with perineal drainage of the bladder, internal urethrotomy being performed at a subsequent operation.

The results are extremely satisfactory, and the operation should be carried out in any case if dilatation is difficult or unsatisfactory. An indwelling catheter for drainage is beneficial and should, unless some complication arises, remain in position four days. Postoperative dilatation is essential.

Chauvin [55] reported a case of ruptured urethra before the Surgical Society of Marseilles.

The patient fell astride a piece of iron. Swelling of the scrotum, hematuria, dysuria and fever occurred. Later there was retention of urine, the penis became edematous and gangrenous, and cystostomy was performed as a preliminary procedure. The perineum was incised with the evacuation of foul-smelling pus. The necrotic tissue was removed and the urethra was opened for a distance of about 3 cm. Three weeks later, when all infection had ceased, the urethra was again explored. It was almost completely closed from 2 cm. behind the meatus to the perineum; the obstruction or stricture was not ring-like as is usual, but was apparently continuous along its length. Only a filiform could be passed. A complete urethrotomy the whole length of the penis was performed. This was followed by a methodical destruction of the hair of the neighboring areas. Later a urethroplasty following Escat's method was done; the new urethra was made with continuous flaps and overlying grafts, for which a portion of the prepuce and a piece of the scrotum was used. In about three weeks a no. 21 catheter could be passed easily, and the canal showed no further tendency to stricture.

An interesting point of jurisprudence is brought up: This man had a gonorrheal stricture before the trauma. It seems logical that the trauma would have been much less severe if it had not been for the presence of the old gonorrheal stricture. The bursting of the urethra occurred in an area of dilatation behind the stricture.

Cecil [56] reports a case of a girl, aged 11, with diurnal and nocturnal incontinence. When the child was 4 years old, she had had a severe pain in the region of the bladder which lasted for several months. Eight months later, she passed a large stone, about 3 by 1.5 cm. Following this incontinence developed. The general examination was negative. It was noted on attempting to examine the genitalia that the child habitually kept the thighs firmly adducted, and when told to walk she was inclined to walk with as little motion

55. Chauvin, E.: Rupture traumatique d'un urethra retreci: Uretroplastie sur une longueur de 10½ cm., Arch. franco-belges de chir. **28**:720-723, 1925.

56. Cecil, A. B.: Destructive Lesions of the Female Urethra in Childhood: A Differential Diagnosis from Female Hypospadias, J. Urol. **14**:441-475 (Nov.) 1925.

of the thighs as possible; she even ran in this manner. Urine constantly dripped from the vulva, both when she was lying down and when she was walking, and the skin surrounding the vulva was excoriated. The labia were held firmly together. The clitoris and labia minora were normal, but there was no evidence of a hymen. The external urethral orifice appeared normal and was in a normal position anteriorly. A soft rubber catheter introduced into this orifice appeared in the vagina, and it was found that the urethra extended back for 1.5 cm. from the external urethral orifice. The urethra easily permitted the passage of a no. 14 catheter. For about 1 cm. the urethra was of normal thickness, but near the vaginal portion it became thinner and almost weblike. The inner portion of the urethra extended from the anterior vaginal wall. At this point its edges were excoriated, and urine salt was adhering to it. Back of this anterior portion of the urethra there was nothing to indicate the urethra except a change in color of a strip of the anterior vaginal wall. There were no lateral walls, nor any tags, nor evidence of scar. With the aid of a speculum, a round opening in the wall of the bladder directly into the vagina was found. The edges of the opening were thin and it was without power to retain urine, remaining constantly open; the whitish bladder wall could be seen flapping against it. The index finger was easily introduced into the vagina. Just above the internal urethral orifice was a constriction which would not permit the easy passage of the finger, and no further attempt was made to do so. By two operations a urethra was constructed which functioned satisfactorily.

Calculi.—Lemperg [57] reports a case of urethral stones in a man, aged 38. The roentgen ray revealed an irregular shadow of a stone, about 2 by 4 cm., in the perineal area. Under local anesthesia, the posterior urethra was split a distance of 2 cm. Eleven stones were removed; the largest was about 7 cm. in diameter. Three of the stones were faceted. The entire group of stones weighed 9.3 Gm., and measured 4.1 cc. by volume.

ANESTHESIA

Papin [58] has employed ethylene gas anesthesia in most of his urologic operations for the last two years; he rarely uses local, regional or spinal anesthesia. A perfect anesthetic must be one that is effective but harmless. Ethylene was found to be much more effective than nitrous oxide, which he had been using for two years. He began using it in animal experimentation and then he used it in man in 700 cases, and found that it presents no disadvantages. Mixed with oxygen, ethylene is administered like nitrous oxide, but correct induction requires experience. Before giving ethylene a subcutaneous injection of pantopon is given to quiet the patient. Anesthesia is complete in from one to twelve minutes, the average being five minutes. Recovery as a rule is quick,

57. Lemperg, Fritz: Harnröhrensteine, Zentralbl. f. Chir. **53**:214-215 (Jan. 23) 1926.

58. Papin, E.: Anesthésie à l'éthylène, XXV Cong. Franç. d'Urol., Presse méd. **2**:1446, 1925.

and there is no vomiting or excitation. Ethylene does not affect the functioning of the kidneys. Patients with nephritis, serious pulmonary and cardiac lesions were operated on successfully.

Papin states that ethylene gas is highly inflammable and when mixed with oxygen explodes with a loud report on coming in contact with a flame, but if the same precautions are taken as with ether, accidents are avoided. Aside from its inflammability, Papin regards ethylene as the best anesthetic in urologic cases.

[Ed. Note.—Ethylene gas is particularly desirable as an anesthetic for urologic surgery. The surgeon finds it most necessary to conserve the remaining function of the kidneys. Dealing as he usually does with aged patients, many of whom have renal lesions, any anesthetic that does not add to the postoperative strain on the kidneys is a desirable asset. According to investigators who have used ethylene in a large number of cases, it does not differ from nitrous oxide in its degree of inflammability. The occasional explosive accidents have had wide publicity. The usual precautions necessary for the safe conduction of a nitrous oxide-oxygen anesthesia are generally also sufficient for ethylene anesthesia. Various methods for preventing static spark explosion have been devised; the simple grounding of the operating table to the floor drain pipe is usually sufficient to guard against this possible igniting factor.]

Shaw [59] reports a study of experimental and clinical data on epidural anesthesia in perineal prostatectomy. Extradural injections of various quantities of methylene blue solution were made in eleven fresh cadavers in an effort to determine the upward extension of solutions injected through the sacral hiatus. It was found that from 15 to 20 cc. completely filled the extradural space in the sacral canal, and that solution in excess of this quantity extended into the thoracic and lumbar regions of the vertebral canal.

A series of 100 cases of perineal prostatectomy performed under extradural nerve block anesthesia are described. Transsacral injections and local infiltration were not employed. The dosage and concentration of the anesthetizing solution underwent variation from time to time, while attempts were made to find the most satisfactory method of producing complete anesthesia with the minimal unfavorable reaction.

Among the 100 cases complete anesthetization failed in 17 per cent. If patients had definite pain the anesthetics were classified as failures, even though the operation was completed without a general anesthetic. A general anesthetic was given in eleven cases.

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59. Shaw, E. C.: Epidural Anesthesia for Perineal Prostatectomy: An Experimental and Clinical Study, with Report of 100 Consecutive Cases, J. Urol. **15**:219-265 (March) 1926.

The incidence of satisfactory anesthesia was not proportional to the amount of procaine solution used, but was proportional to the concentration of the solution. The best results were obtained with from 15 to 20 cc. of 3 per cent procaine. The percentage of failure was not only reduced, but the anesthesia was more complete.

Blood pressure determinations, as well as pulse and respiration rates, were made in all cases at five minute intervals from the time of injection to the completion of the operation. The blood pressure was found to be the best indication of the patient's condition. The systolic blood pressure frequently fell from 30 to 50 mm. with no change in the patient's appearance.

Two distinct types of reaction were observed. One consisted of increase in blood pressure and pulse rate, and in excitability and convulsive movements, apparently due to general procaine intoxication resulting from absorption of the drug into the blood stream. This type was rare, being observed in only two cases. The second type consisted in decrease in blood pressure, slowing of the pulse rate and extreme weakness, occurred much more frequently, and was probably due to the localized paralytic action of the excessive amount of solution on the sympathetic nerves making their exit from the cord in the thoracic and upper lumbar segments. Practically no reaction occurred if the patients received from 15 to 20 cc. of 3 per cent procaine.

The ultimate mortality rate in the 100 cases was 3 per cent. None of the deaths was attributable to the anesthetic.

Extradural anesthesia produces complete relaxation of the muscles of the perineum, thereby facilitating the operation. The postoperative complications are definitely less than those following any type of general anesthesia. Postoperative pneumonia and uremia did not occur. There was only one case in which cardiac decompensation developed. This was mild and the patient recovered. Supplementing extradural block with transsacral injection is unnecessary.

Epidural anesthesia should not be used in nervous uncooperative patients unless general anesthesia is definitely contraindicated. Among younger patients in good general condition, the choice of an anesthetic is of no great importance, but among old, debilitated patients with impaired renal function, extradural anesthesia undoubtedly reduces the operative risk.

[Ed. Note.—Shaw states that it is not necessary to supplement the extradural block with transsacral injections; he reports 17 per cent of failures. In a recent report by Meeker and Scholl, 270 cases of prostatectomy under transsacral anesthesia are reported with only 5.8 per cent of failures. In a large series of cases it was found that simple epidural injections were unreliable and resulted in failure too frequently.

The transsacral blocking is more difficult and requires more time for injection, but the patient is ready for operation immediately after administration of the anesthetic without the delay necessary following the single caudal injection.

In a series of more than 1,800 cases, Meeker and Scholl [60] found a 1 per cent solution to be the most satisfactory. In a series of 500 cases, mostly simple caudal injections, the strength of the solution was from 2 to 3 per cent; in these cases reactions were much more common and the anesthesia was not as satisfactory as when a 1 per cent solution was employed.

Regardless of the technic of the method employed, the introduction of sacral anesthesia has unquestionably been a factor in the lowering of the operative mortality rate following prostatectomy. The operative mortality rate in cases in which sacral anesthesia was employed is less than half that following prostatectomy under either ether or spinal anesthetics. In patients recovering from operation, there was no difference in the late results following the different types of anesthetics. Sacral anesthesia does not entirely eliminate the possibility of respiratory infection; when this occurs following the administration of ether it is usually attributed to pulmonary irritation from the anesthetic. Sacral anesthesia definitely eliminates the group of immediate deaths usually attributed to shock and cardiac disease.]

Bilger [61] reports a series of cases of epidural anesthesia used in Marion's urologic service. It was successful in seventeen cases, partially successful in two, and a failure in six. No accidents were noticed, although one patient had a slight collapse, and another had a marked sensation of cold in the lower extremities followed by intense trembling. Some inconveniences may be encountered in the obese patient, as the landmarks may be difficult to find. Anatomic anomalies, such as an exaggerated curvature of the sacrum, ossification of the membrane or narrowness of the sacrococcygeal hiatus may be present. Sacral nerve blocking is of definite benefit when a general anesthetic cannot be used, for old people and for patients with arteriosclerosis and pulmonary, cardiac or cardiorenal disease. There is less danger than with spinal anesthesia; it lasts at least two hours and there is no postoperative pain. This method of anesthesia is especially indicated in all operations on the urethra and in the bladder, except litholapaxy. In ten patients with prostatic disease operated on by Marion, definite success followed in only five. The prostate sometimes remains sensitive. Should the

60. Meeker, W. R., and Scholl, A. J.: Sacral Nerve Block Anesthesia, Ann. Surg. **80**:739-772 (Nov.) 1924.

61. Bilger, F.: De l'anesthésia épidurale en chirurgie urinaire, J. d'urol. **19**:111-126 (Feb.) 1925.

anesthesia be perfect, other disadvantages may present themselves: (1) It may be necessary to make a separate field block for the skin; (2) the rigidity of the abdominal muscles may prevent satisfactory exposure; (3) enucleation of small and hard nodules may provoke a painful pulling sensation of the peritoneum, which is nevertheless bearable, and (4) the nervous state of the patient may be an obstacle to the good results.

UROGRAPHY

Braasch [62] reviews the difficulties arising from the interpretation of pyelograms. He states that correct interpretation of a pyelogram is based on familiarity with the outline of the normal pelvis. Unless one is thoroughly familiar with the possible variations in the outline of the normal pelvis, it is difficult to recognize deformity.

Incomplete filling of the pelvis and calices is a frequent source of error in interpretation. Unless the outline is complete, the apparent deformity may be taken for neoplasm or cortical necrosis. On the other hand, as the result of insufficient distention, hydronephrosis, anomaly and other lesions may easily be overlooked. Certain renal pelves are particularly difficult to outline, as repeated attempts may show. There is a marked difference in the rapidity with which the pelvis empties itself following distention with the pyelographic medium. If the pelvis is spastic a pyelogram made a short time after distention will usually show only a partially outlined pelvis, whereas in other types the medium may be retained and may outline the entire pelvis for several minutes after the injection. Blood clots may cause apparent filling defects in the outline, which are suggestive of neoplasm or soft stone. Postoperative deformity such as results from removal of stones, fixation of a kidney, drainage and exploration is often confusing.

Correct interpretation of the outline of the ureter is particularly difficult, and the personal equation is important. Irregularities in the outline of the ureter have been variously interpreted, and the diagnosis of stricture, kinks and pathologic irregularities has been made with comparatively little accurate basis for such interpretation. The elasticity and distensibility of the ureter is not generally recognized. Areas of apparent dilatation are readily outlined in the normal ureterogram as a result of localized areas of overdistention. On the other hand, the ureter may actually be dilated, and when incompletely filled gives a similar appearance. Complete uniform distention of the ureter is essential to correct interpretation, as in the renal pelvis. This, however, may be difficult, and although a number of suggestions have been made with regard to methods of securing uniform distention, they are not always

62. Braasch, W. F.: Errors in the Interpretation of Urographic Findings, J. Urol. **14**:631-639 (Dec.) 1925.

successful. Introduction of the ureteral catheter, either equipped with a bulb or of such size that the ureter is occluded for a short distance beyond the ureteral orifice, will usually permit the medium to outline the entire ureter. The introduction of two catheters, one into the renal pelvis and the other into the lower ureter, with simultaneous injection, will also accomplish this. In doubtful cases, a subsequent ureterogram should be made, unless there are clinical contraindications.

Hunner has shown that actual stricture of the ureter is more common than has been previously supposed, particularly in cases of chronic pyelonephritis. That it is often the cause of obscure abdominal pain and of various renal lesions is not borne out by pathologic, urographic and clinical evidence. Stricture causes definite dilatation of the ureter, and a variable degree of pyelectasis is also usually present. With stricture in the lower portion of the ureter, the dilatation in the pelvis is predominant in the ends of the calices. Apparent kinks in the ureter may be caused by the outline of two superimposed portions of a redundant ureter.

Ureteral spasm will probably explain many cases of so-called ureteral stricture diagnosed by means of ureteral bulbs. It may also explain the divergence between such clinical diagnoses and the results on surgical or postmortem examination.

The recognition of renal neoplasm offers one of the most difficult problems in pyelographic interpretation. It is difficult to distinguish between the unusual normal pelvis, the pelvis which is incompletely distended, and filling defects caused by blood clots.

An interesting problem of differentiation arises when the ureter is outlined as far as the ureteropelvic juncture and there is no evidence of the pyelographic medium above this point; in other words, when there is apparent occlusion of the ureter at this point. This may occur with hydronephrosis, renal tuberculosis, neoplasm, atrophic pyelonephritis, anomaly and lithiasis. The diagnosis of any of these conditions is necessarily largely dependent on other cystoscopic and clinical data, and may be impossible from urographic interpretation alone.

Frontz [63] believes that ureteropyelography may be regarded as a safe procedure with the introduction of nontoxic opaque mediums, provided the pelvis is not overdistended in filling. The filling is best done by the gravity method. Bilateral pyelograms may be justified in a few cases in which the renal function is not impaired, but this should not be a usual procedure. Most satisfactory films will be obtained, and with less risk and discomfort, if one side at a time is examined.

It is most essential in interpreting pyelograms that the variations from normal be clearly understood. The realization that the ureter is

63. Frontz, W. A.: Errors of Technique and Interpretation in Ureteropyelography, J. Urol. **14**:579-592 (Dec.) 1925.

an easily distensible muscular tube, conveying the urine from the kidney to the bladder by peristaltic waves similar to those of the intestine, will explain many variations in the ureteral outline which are often erroneously interpreted as due to strictures.

The diagnosis of ureteral stricture is not justifiable unless the ureterogram reveals a definite pathologic dilatation above the suspected area. The dilatation is abrupt and not the fusiform swelling which is the normally wide lumen above the "ring muscle" or a phase in a peristaltic wave.

In certain cases of hydro-ureter, sometimes associated with hydronephrosis, there is no demonstrable obstruction either in the upper or lower urinary tract. The bladder is large, and the ureteral orifices frequently dilated, so that when a cystogram is obtained the opaque medium enters the upper tract. In certain cases only the lower ureter is dilated; in others, the entire ureter and the renal pelvis are involved. No adequate explanation is offered for the loss of integrity of the ureteral and pelvic musculature in these cases.

The diagnosis of ureteral stricture is not justifiable unless the ureter-rendered uncertain by the presence of a phlebolith or calcified glands which lie in the same plane as the ureter. Definite dilatation shown in the ureterogram, even though it is above the level of the suspected shadow of stone, may be produced by stricture. The only certain and absolute method for diagnosing the condition is by means of stereoscopic ureterography.

The possibility of error in the diagnosis of renal tumor will be considerably lessened by careful consideration of factors which may produce a pelvic outline simulating that caused by tumor. A blood clot may produce a filling defect, and a pelvis incompletely filled or in spasm may prove misleading.

Braasch and Carman [64] state than in cases of renal tumor simple radiography may reveal: (1) symmetrical enlargement of the renal shadow; (2) local projections of its contour; (3) areas of moderately increased density within a renal shadow of normal size and form; (4) partial or complete concealment of the renal shadow by the shadow of the tumor, or (5) localized density due to calcified areas in the tumor, or to calculi which are sometimes associated with the tumors. Occasionally fimbriated streaks of calcification are found which are almost pathognomonic of hypernephroma. A large tumor of the kidney may displace the adjacent segment of the colon or thin its opaque contents by pressure. At times secondary tumor deposits in the chest or osseous system may furnish the first clue to a malignant tumor of the

64. Braasch, W. F., and Carman, R. D.: The Pyelographic and Roentgenologic Diagnosis of Renal Tumors, Radiology **4**:445-452 (June) 1925.

kidney. Pneumoradiography and pneumoperitoneal roentgenography may be of distinct advantage in outlining the kidney, but there is some hazard attached to the procedure and it is not advisable as a routine. Changes in the pyelogram resulting from neoplasms and cysts include: (1) elongation of one or more calices, or of the true pelvis; (2) shortening of the calices; (3) encroachment on the pelvic lumen causing flattening of the pelvic contour, narrowing of individual calices, obliteration of one or more calices, or obliteration of the true pelvis; (4) broadening of the calices; (5) pyelectasis; (6) displacement of the pelvis, and (7) deformity of the ureteropelvic juncture. As the tumor extends peripherally it draws the calix out with it. The number of calices involved increases with the size of the tumor. When several calices are affected, the growth has usually invaded the greater portion of the kidney.

Eisendrath,[65] in describing errors which may arise in the diagnosis of renal tumors by pyelograms, draws attention to the several other causes in which the pyelogram will simulate that of tumor. Spider deformity is the result of compression, elongation or distortion of the pelvis proper and its major and minor calices. That it can take place as the result of conditions such as acute suppurative or more chronic fibrous perinephritis, and even of an atrophic pyelonephritis, is not generally appreciated. When well marked, this alternation of the calices is valuable evidence of an intrarenal neoplasm invading or compressing the pelvis or its calices. If one distends the lumen completely and can eliminate a possible spasm or other form of temporary or permanent closure of the neck of the calix, this pyelographic change is dependable.

A neoplasm situated at the pelvic outlet, either blocking it from within or compressing it from without, can cause retention of intrapelvic contents in a manner similar to any other obstruction which causes ordinary aseptic or infected hydronephrosis.

The study of changes due to perirenal conditions and atrophic pyelonephritis has been developed so recently that it is desirable to call attention to it. If the perirenal compression is in intimate relation to the parenchyma, the effect is chiefly to distort the pelvis and calices. If, however, the cause of compression is more distant, such as retroperitoneal sarcoma, the ureter is more likely to be displaced outward or inward, and there is more or less renal torsion.

Lower and Belcher,[66] in their summary of urographic studies of pathologic conditions of the ureter, recommend that, rather than attempt to get a pyelo-ureterogram by first injecting the pelvis and then partly

65. Eistendrath, D. N., and Koll, I. S.: Pyelographic Errors in the Diagnosis of Renal Neoplasms, J. Urol. **14**:615-629 (Dec.) 1925.

66. Lower, W. E., and Belcher, G. W.: Urographic Studies of Ureters, J. Urol. **14**:593-614 (Dec.) 1925.

withdrawing the catheter while filling the ureter, the pyelogram and ureterogram should be taken separately. In this manner both pictures will be more accurate. They make a plea for the use of stereoscopic ureterograms whenever feasible. The points of normal narrowing must be borne in mind, as well as the effect of peristalsis. Careful filling is of greatest importance, and small defects should be rechecked before conclusions are made.

Lower's procedure for passing a catheter through an otherwise impassable stricture is as follows: A no. 5 or 6 French radiographic ureteral catheter is passed up the ureter to the point of obstruction. A roentgenogram is then taken, but does not reveal the cause of obstruction.

Carefully keeping the tip of the radiographic ureteral catheter against the point of obstruction, a no. 4 French nonradiographic, olivary tipped catheter is passed up the ureter alongside the radiographic catheter. Then, as one filiform is passed by the other through filiform strictures of the ureter, the no. 4 nonradiographic catheter is passed into the stricture and along the strictured ureter into the dilated ureter above. At this point the retained urine is drawn off and the kidney function ascertained.

This being accomplished, another ureterogram is made. This second ureterogram gives the exact length of the stricture, since the shadow cast by the catheter does not fuse with that of the opaque fluid in the dilated ureter above the stricture.

Graves,[67] in a review of the various substances used as pyelographic mediums, points out that any overdistention of the renal pelvis may cause prompt invasion of the local and general circulations. The pyelographic medium, then, becomes potentially an intravenous injection. Because of this and the undesirable physical properties of the silver colloids these preparations were abandoned, and were followed by thorium nitrate, which in time was replaced by more easily prepared and less expensive substances, namely, sodium iodide and sodium bromide. At the present time sodium iodide in 12 per cent solution is probably the most widely used medium.

Graves reports laboratory experiments and clinical evidence in favor of 12 per cent sodium iodide, and advises the addition of mercuric iodide to make a dilution of 1:3,000 mercuric iodide in 12 per cent sodium iodide, to render the medium antiseptic.

UROLOGIC DIAGNOSIS IN CHILDREN

Patch[68] reviews several histories which show the applicability of modern urologic methods to small children.

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67. Graves, R. C.: Pyelographic Media, J. Urol. **14**:571-578 (Dec.) 1925.

68. Patch, F. S.: The Applicability of Urological Methods of Diagnosis and Treatment to Infants and Children, Canad. M. A. J. **15**:8-14 (Jan.) 1925.

He first cites the case of a boy, aged 4 years, who had pyuria with difficult and painful urination. Rectal examination revealed a hard mass in the region of the prostate; roentgen-ray examination showed this mass to cast a shadow of a stone, probably in the urethra. A few days later, the stone became impacted at the penoscrotal angle and was removed by external urethrotomy. The roentgen ray also revealed shadows in the area of the left kidney. Cystoscopy assisted in making a diagnosis of calculus. Nephrectomy was performed with good results. Another boy, aged 9½ years, had pyuria, fever, a small meatus and a stricture in the penile urethra. These strictures were dilated, and cystoscopic examination revealed a stone in the bladder. This was removed suprapubically. The obstruction had been undiagnosed for eight years. Another boy, aged 8 years, had incontinence of urine. Circumcision had been done previously without improvement. When seen by Patch he had acute pyelonephritis, with fever and pyuria, and the bladder was distended to the umbilicus. He was anemic. A small meatus was found, and a gradual decompression of the bladder and cystoscopy were done. The bladder was kept empty and the patient gradually improved.

In reviewing the cases presented, one cannot help noting the predominance of two factors, one of obstruction, the other of infection. If the cause is removed cure follows, unless damage of vital organs by infection has progressed to such a degree that restitution to normal is impossible. It is obvious, therefore, that if one wishes to deal rationally with pathologic conditions in the urinary tract an early and thorough examination must be made. If we admit the necessity of a thorough urologic examination in adults having symptoms of urinary trouble, it is logical that children should have the same advantages, particularly as examination frequently offers the only means of detecting the underlying etiologic factors in the production of the pathologic changes. Unless the cause and exact conditions are known, any treatment must be largely empirical and is often misdirected. That the urinary tract of children, and even of infants, is capable of being examined thoroughly by urologic methods has been amply demonstrated.

[Ed. Note.—The relationship between the urologist and the pediatrician now is about the same as it was between the urologist and the internist or surgeon a decade or more ago. A cystoscopic examination then seemed to the internist to be a formidable procedure for the patient and at times of questionable value. The internist now realizes that urologic examinations offer invaluable assistance in the diagnosis of certain obscure conditions. It is hoped that such reports as those of Patch, Kretschmer, Helmholz and Hinman will encourage cooperation between the urologist and the pediatrician.]

PHLEBOLITHS

Culligan [69] reports that 38.99 per cent of the roentgenograms of the pelvis taken at the Mayo Clinic show shadows of phleboliths. The

69. Culligan, J. M.: Phleboliths, J. Urol. **15**:175-188 (Feb.) 1926.

shadows are more common in males than in females. Forty-seven per cent of shadows of phleboliths were bilateral.

The phleboliths vary between 1 and 10 mm. in diameter, the average being about 4 mm. They are usually found in the periprostatic plexus of males and in the uterine plexus of females; occasionally they are found in splenic veins and in the veins of hemangiomas. Microscopically phleboliths are strikingly uniform, the main difference being that the larger ones show areas of ossification. Their chemical analysis shows that they contain practically uniform ingredients.

Phleboliths originate in thrombi. The chief factors in their formation are lack of muscular support to the veins, stasis, undernourishment, infection and calcification. They are of particular interest to the urologist as they are easily confused with ureteral stones. The lead catheter is unreliable in localizing pelvic shadows. Pyelo-ureterography is the most accurate method for localizing questionable pelvic shadows. The perivesical plexus containing phleboliths and thrombi is an ever ready focus for emboli.

[ED. NOTE.—The pyelo-ureterogram is unquestionably the most accurate method of differentiation of ureteral shadows but pyelography always entails a slight but definite risk, usually not associated with simple ureteral catheterization. Stereoscopic roentgenography may be satisfactorily employed in many cases.]

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